JOC The Journal of Organic Chemistry

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Access to Spiro Bis-β-lactams via a Metal-Free Microwave-Assisted Wolff Rearrangement/Staudinger [2+2] Cycloaddition Cascade Involving 3-Diazotetramic Acids and Imines

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Cite This: https://doi.org/10.1021/acs.joc.3c02494 Read Online

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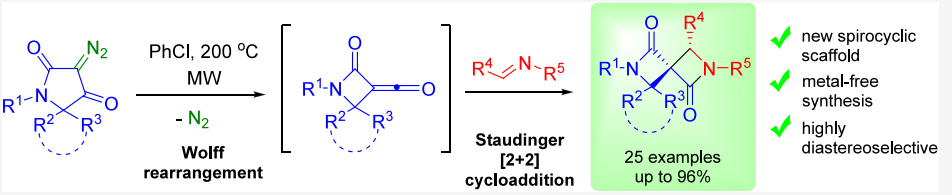

ABSTRACT: Herein, we report the study of the thermally promoted reaction of 3-diazotetramic acids with imines as a rapid route to a novel spiro heterocyclic scaffold, spiro bis-β-lactams (2,6-diazaspiro[3.3]heptane-1,5-diones). The transformation proceeds via metal-free microwave-assisted Wolff rearrangement of the diazo reagent followed by Staudinger [2+2] cycloaddition of the heterocyclic ketenes with Shiff bases. This methodology enables the preparation of diastereomerically pure spiro bis-β-lactams in high yields and provides an avenue for exploring new versions of the privileged β-lactam core for drug design.

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There is no doubt that the development of new heterocyclic scaffolds is one of the most important components of modern drug design. New, previously unexplored molecular frameworks may possess attractive physicochemical and biological profiles from a medicinal chemistry perspective. Some of the most sought-after motifs are spirocyclic structures.[1] Indeed, spirocycles possess a pronounced spatial character and degree of saturation that distinguish them from flat aromatic heterocycles (the traditional building blocks for drug discovery).[2] Spirocycles thus address two important trends in modern drug design: the tendency to create more "three-dimensional" scaffolds[3,4] and the increased preference for molecules with more sp^3-hybridized atoms (higher Fsp^3 compounds).[5,6]

β-Lactams (2-azetidinones) are well established as privileged motifs for drug design.[7−11] This necessitates the availability of convenient methods for the synthesis of β-lactams with any conceivable substitution pattern and makes the development of synthetic methodologies toward spirocyclic β-lactam frameworks a highly worthy goal.

The Wolff rearrangement/Staudinger [2+2] cycloaddition cascade involving diazocarbonyl reagents is a powerful and actively evolving tool for producing β-lactams.[12−15] However, there have been only a few examples in the literature of the use of cyclic diazo compounds for the construction of spirocyclic β-lactams.[16−18] Continuing our research in the field of developing approaches to the construction of spirocyclic scaffolds based on transformations of diazo heterocycles,[19−22] we turned to the chemistry of diazo tetramic acids. It has been found that the Wolff rearrangement of these diazo reagents has been investigated infrequently. In the literature, there are only a few examples of the photolytic decomposition of diazo tetramic acids in the presence of some O- and N-nucleophiles, published ∼50 years ago by Lowe and co-workers[23,24] and Stork and Szajewski.[25]

In this work, we present an efficient approach to the construction of a new spirocyclic bis-β-lactam scaffold with promising potential for further exploration in biochemical studies. The method is based on the thermally promoted Wolff rearrangement of diazo tetramic acids in the presence of different imines.

The initial attempt to realize the thermal cyclocondensation of diazo tetramic acid **1a** with imine **2a** turned out to be successful and was performed as follows. The mixture of reagents was stirred in a closed vessel under conventional heating at 80 °C with a gradual increase in temperature while the presence of the diazo reagent was monitored by thin layer chromatography. It should be noted that the diazo tetramic derivative proved to be very resistant to thermal treatment, and only when it was heated at 200 °C for 3 h was almost complete consumption of diazo tetramic acid **1a** observed. The reaction afforded spirocyclic bis-β-lactam **3a** in 72% yield as a single diastereomer (structure confirmed by X-ray analysis data)

Received: October 31, 2023
Revised: January 11, 2024
Accepted: January 26, 2024

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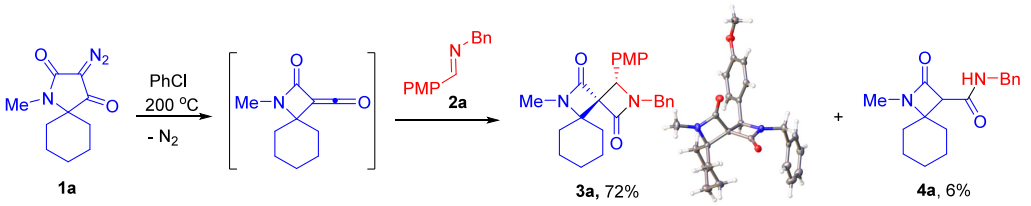
Scheme 1. First Thermal Decomposition of Diazo Tetramic Acid 1a in the Presence of Imine 2a[a]



[a]Reaction conditions: **1a** (0.25 mmol) and **2a** (0.25 mmol) in dry PhCl (1 mL) at 200 °C for 3 h. PMP = *p*-methoxyphenyl.

(Scheme 1). In addition, amide **4a** was also isolated as a byproduct. Its formation can be related to the partial hydrolysis of imine **2a** (or some imine-derived intermediate) under the action of residual traces of moisture.

The formation of **3a** is due to the initial contraction of the diazo derivative pyrrolidone cycle during the Wolff rearrangement (formation of the first *β*-lactam fragment), followed by [2+2] cycloaddition of the intermediate ketene to imine **2a** (formation of the second *β*-lactam ring). The resulting spiro-conjugated bis-*β*-lactam is a representative of a hitherto unknown class of spiro heterocycles.

Carrying out Wolff rearrangement under microwave irradiation has previously been shown to have several advantages.[26,27] For example, in our case, using microwave-assisted decomposition of diazo tetramic acids, we observed some acceleration of the reaction compared to the reaction with conventional heating, less tar formation, and better reproducibility. Therefore, we switched to using microwave activation for all subsequent experiments. We found that using any of the reagents in excess had no significant effect on the reaction yield. Thus, we decided to use 1.1 equiv of imine as a more readily available reagent.

Next, we started exploring a wide scope of different substrates, diazo tetramic acids **1** (synthesized as described previously[28,29]) and imines **2**, in the Wolff rearrangement/Staudinger [2+2] cycloaddition cascade, delivering polysubstituted spiro bis-*β*-lactams **3** (Table 1).

As one can see from the results of reactions with imine **2a** as well as some other imines, 5,5-disubstituted (spirocyclic and *gem*-dimethyl) diazo tetramic acids give good (for **3a**, **3c**−**f**, **3r**, and **3s**) or excellent (for **3b**, **3h**, and **3u**) yields of the target compounds. At the same time, the yields of products **3g** and **3p** obtained from 5-nonsubstituted diazo derivatives were significantly lower. This may be due to the greater stability (lower reactivity) of the spirocyclic (or *gem*-dimethyl-substituted) ketene intermediate compared to that of the unsubstituted analogue and the stronger tendency of the latter to participate in side processes. The possibility that this may also be due to the relatively lower stability of the less substituted *β*-lactams under harsh synthesis conditions cannot be excluded. The synthesis of **3h** was additionally performed on a 4-fold scale (1 mmol) and yielded 82%.

With regard to the influence of the structure of imine **2** on the result of the reaction, it can be noted that the transition from aliphatic to aromatic substituents on the nitrogen atom of the Schiff base negatively affects the yield of target *β*-lactams (see Table 1, examples **3i** and **3j**). This effect is aggravated by the introduction of an electron-withdrawing substituent into the aldehyde part of the imine (see **3k**).

To our delight, most of the *β*-lactams **3** successfully synthesized in this study were obtained almost exclusively as a single diastereomer, which was confirmed by single-crystal X-ray diffraction data (for **3b**, **3d**, **3i**, **3j**, **3m**, and **3p**) to have the carbonyl group of the first formed *β*-lactam ring and the imine-derived R^3 group on the same face of the second formed *β*-lactam ring. It should also be noted that the presence of an electron-withdrawing substituent in the imine structure leads to a decrease in the diastereoselectivity of the process (examples of **3k**, **3o**, and **3w**).

As has been shown previously, imines from enolizable aliphatic aldehydes cannot give *β*-lactams via a tandem thermal Wolff rearrangement/Staudinger reaction.[14] Some of the few examples of imines with an aliphatic aldehyde moiety that are not prone to tautomeric transition to the enamine form are the derivatives of cyclopropane carbaldehyde. Using this substrate, spiro bis-*β*-lactam **3m** was obtained in a moderate yield and high diastereomeric purity.

The use of 5-monosubstituted diazo tetramic acids (without a plane of symmetry) **1m** and **1n** in the synthesis leads to the formation of target compounds with a third stereogenic center (Table 2). The reaction with 5-phenyl diazo tetramic derivative **1m** proceeds with good control of the diastereoselectivity with respect to the additional chiral center, giving a ratio of diastereomers in the crude reaction mixture of 85:15 [according to nuclear magnetic resonance (NMR)]. Main diastereomers **3x** and **3y** were isolated individually in good yields after chromatography. The relative configuration of the stereocenter, indicated by an asterisk in **3x** and **3y** (Table 2), was assigned on the basis of the analysis of the ^{1}H NMR data as follows.

According to X-ray diffraction data for other bis-*β*-lactams **3**, the spiro-annulated four-membered rings have an almost flat geometry (Figure 1). In the main diastereomer, proton H^a is located near the phenyl substituent attached to the second *β*-lactam cycle and falls within the magnetic shielding area of the aromatic ring. This leads to a shift of the H^a proton signal to the upfield region. As a result, the shifts of protons H^a and H^b differ by ∼1 ppm. In the minor diastereomer, the phenyl substituent is far from the H^a proton and does not significantly affect the chemical shift. As a result, the shifts of the H^a and H^b protons appear to be very similar given their virtually identical chemical environment. A much lower diastereoselectivity was observed in the case of diazo tetramic acid with an adamantyl substituent (**1n**). Product **3z** was isolated in high yield but as a mixture of diastereomers. The assignment of their geometry was made on the basis of the NOESY spectrum (see the Supporting Information).

Some substrates proved to be unsuitable for use in the tandem transformations considered (Figure 2). For example, for two bicyclic diazo tetramic acids, **1o** and **1p**, the reaction resulted in the formation of complex reaction mixtures that did not contain significant amounts of the target product.

https://doi.org/10.1021/acs.joc.3c02494
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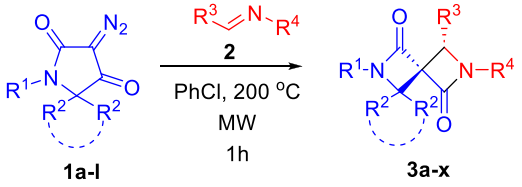
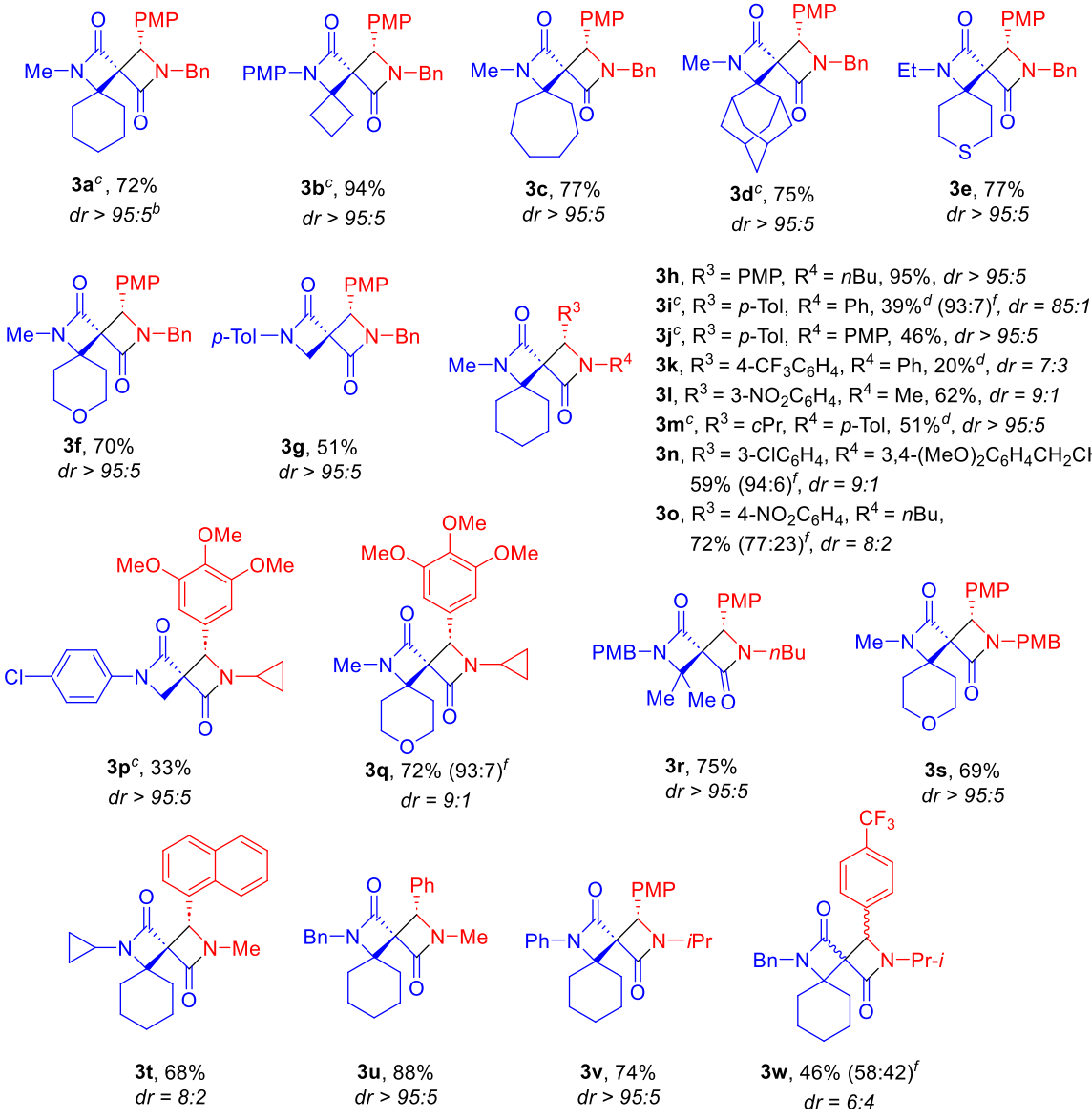
Table 1. Scope for the Synthesis of Spiro Bis-β-lactams 3[a]





[a]Reaction conditions: **1** (0.25 mmol) and **2** (0.28 mmol) in dry PhCl (1 mL) at 200 °C (MW) for 1 h. Isolated yields. PMP = *p*-methoxyphenyl. PMB = *p*-methoxybenzyl. [b]The dr is the diastereomeric ratio in the reaction mixture. [c]Single-crystal X-ray analysis data were obtained (see the Supporting Information). [d]The main side product detected by NMR was the corresponding amide **4**. [f]The ratio of diastereomers in the isolated substance is indicated in parentheses.

Apparently, this is because the fused β-lactam cycle that formed as a result of the Wolff rearrangement is too strained and insufficiently stable under the conditions of synthesis. The same assumption may explain the negative result of the reaction with cyclic imine **2p**.

A plausible mechanism contributing to the stereochemistry of the resulting products **3** is consistent with earlier studies on the Staudinger reaction by Xu and co-workers.[30−32] The process involves the interaction of cyclic acyl ketenes with the imine (predominantly *E* form) from the acyl side resulting in a zwitterionic intermediate (Scheme 2). The presence of an acyl group in ketene and the introduction of a strongly electron-donating (*p*-methoxyphenyl) group in the iminium moiety disfavor direct ring closure, and subsequently, isomerization occurs. The diastereomeric zwitterion undergoes fast con-rotatory cyclization, giving "*cis*"-β-lactams **3a−h**, **3r**, **3s**, and **3v**

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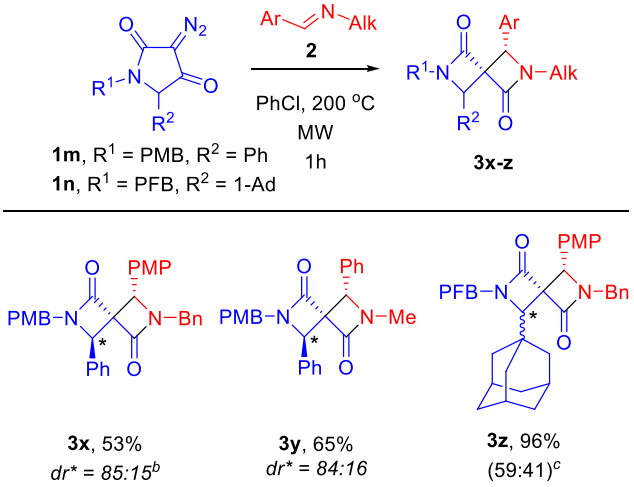
Table 2. Examples with 5-Monosubstituted Diazo Tetramic Acids[a]



[a]Reaction conditions: **1** (0.25 mmol) and **2** (0.28 mmol) in dry PhCl (1 mL) at 200 °C (MW) for 1 h. Isolated yields. PMP = *p*-methoxyphenyl. PMB = *p*-methoxybenzyl. PFB = *p*-fluorobenzyl. 1-Ad = 1-adamantyl. [b]The dr* is the diastereomeric ratio in the reaction mixture. [c]The ratio of diastereomers in the isolated substance is indicated in parentheses.

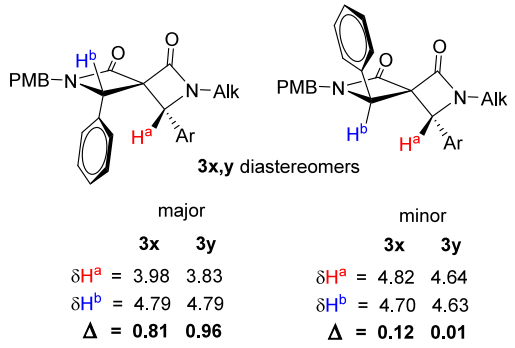


Figure 1. Geometry of diastereomers for **3x** and **3y**.

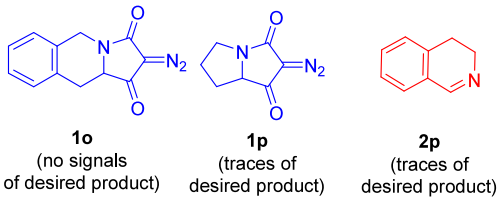
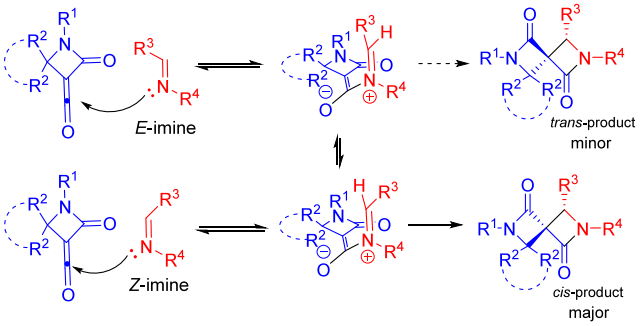


Figure 2. Incompatible substrates (no target product was obtained).

with high diastereoselectivity. At the same time, electron-withdrawing substituents in the aromatic ring or bulky groups at the nitrogen atom of imine hinder the isomerization, leading to its competition with the direct ring closure and the formation of diastereomeric mixtures. Notably, a pronounced effect is observed for **3w**, and to a lesser extent for **3k**, **3l**, **3n**, **3o**, and **3w**. Additional heating of the obtained diastereomeric mixture of **3w** (at 200 °C in PhCl for 1 h) leads to only a slight epimerization (dr 58:42 → 62:38). With a longer heating time (7 h), a significant decomposition of the target compound was observed.

Scheme 2. Plausible Mechanism for the Staudinger [2+2] Cycloaddition Step of the Process



In summary, this work proposes an efficient approach to the construction of a novel spirocyclic bis-*β*-lactam scaffold. The method is based on a metal-free microwave-assisted Wolff rearrangement/Staudinger reaction sequence involving diazo tetramic acids and Schiff bases. In most cases, the reaction proceeds with high diastereoselectivity, and in some cases, the configuration of three stereocenters can be controlled simultaneously. This method is of a general nature and provides rapid access to medicinally relevant spiro and polyspiro heterocyclic structures with a diverse periphery.

■ 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.joc.3c02494.

Experimental procedures, compound characterization data, and X-ray crystallographic information (PDF)

Accession Codes

CCDC 2193240, 2293694, 2299542, and 2299544−2299548 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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https://doi.org/10.1021/acs.joc.3c02494
J. Org. Chem. XXXX, XXX, XXX−XXX

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors are grateful to the Russian Science Foundation for financial support (Project Grant 20-13-00024). The authors thank the Research Centre for Magnetic Resonance, the Center for Chemical Analysis and Materials Research, and the Centre for X-ray Diffraction Methods of Saint Petersburg State University Research Park for obtaining the analytical data.

■ DEDICATION

Dedicated to the 300th anniversary of Saint Petersburg State University's founding.

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