OL Organic Letters

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Formation of 6-Azaindoles by Intramolecular Diels–Alder Reaction of Oxazoles and Total Synthesis of Marinoquinoline A

Mana Osano, Dishit P. Jhaveri, and Peter Wipf*

Cite This: https://dx.doi.org/10.1021/acs.orglett.0c00417 Read Online

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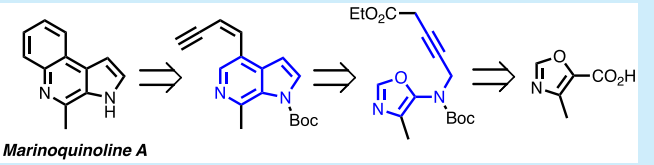
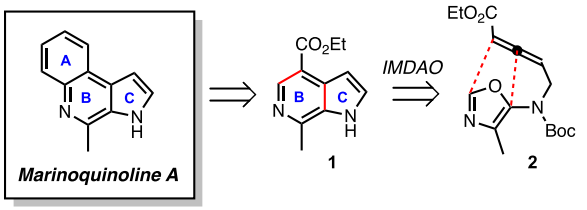
ABSTRACT: A new variant of the intramolecular Diels–Alder oxazole (IMDAO) cycloaddition that provides direct access to 6-azaindoles was developed. The IMDAO reaction was applied in a total synthesis of the aminophenylpyrrole-derived alkaloid marinoquinoline A, also featuring the use of a Curtius reaction for preparation of a 5-aminooxazole, a propargylic C,H-bond insertion, an *in situ* alkyne–allene isomerization, and a ruthenium-catalyzed cycloisomerization for benzene ring annulation to the 6-azaindole.



The intramolecular hetero-Diels–Alder reaction is a versatile method for generating monocyclic and polycyclic heteroarenes,[1] including pyridines,[2−4] pyrimidines,[5,6] quinolines,[7,8] and isoquinolines,[9,10] and has frequently been applied to complex target molecule synthesis.[11] As an extension of our intramolecular Diels–Alder furan (IMDAF) reaction for indole synthesis,[12,13] we now report a new variant of the intramolecular Diels–Alder oxazole (IMDAO) cycloaddition,[14,15] leading to 6-azaindoles. Furthermore, we apply this new reaction to the preparation of the pyrroloquinoline marinoquinoline A (Scheme 1).

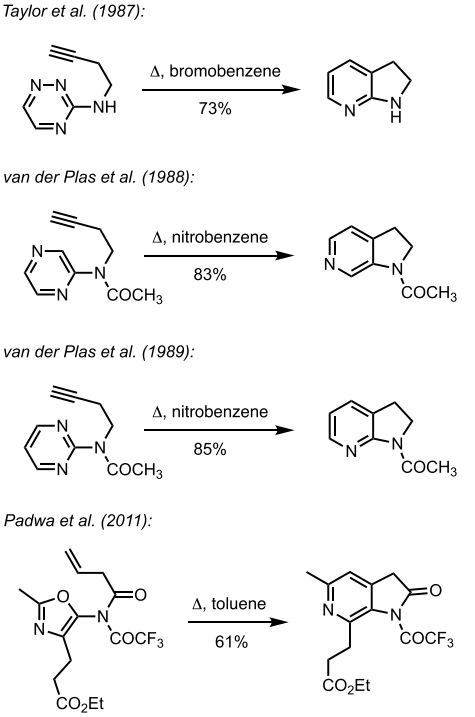
Scheme 1. Retrosynthetic Approach to Marinoquinoline A Using a Key Intramolecular Diels–Alder Oxazole (IMDAO) Cycloaddition of Allenoate 2 to Generate the B–C Ring 6-Azaindole 1



IMDAO reactions are well-established in the heterocyclic literature[16] and have previously been used in natural product synthesis.[17−19] However, to the best of our knowledge, this is the first application of this Diels–Alder variant for 6-azaindole synthesis, with the exception of some precedent for the generation of partially saturated heterocycles containing this core structure (Scheme 2).[20−23]

We had previously identified conditions for a Diels–Alder cycloaddition route to indoles **4** from allenyl furans **3**, but when we applied analogous conditions to oxazoles **5**, we encountered experimental challenges with the preparation and

Scheme 2. Previous Intramolecular Diels–Alder Reactions in Azaindolin(on)e Syntheses



Received: February 1, 2020

https://dx.doi.org/10.1021/acs.orglett.0c00417
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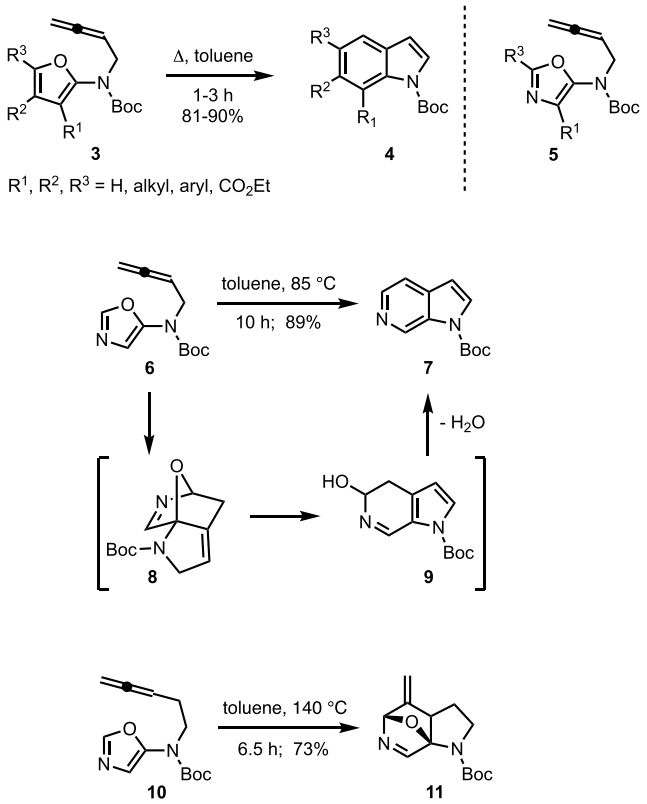
isolation of these allenyl oxazoles with substituents in the R^1 and R^3 positions (Scheme 3).[24] In contrast, in toluene at 85 °C, the monosubstituted allenyl oxazole **6** provided the desired 6-azaindole **7** in 89% yield, presumably via the bridged bicyclic intermediate **8** followed by the partially eliminated pyrrole **9**. Significant support for this mechanism stems from the isolation of the oxygen-bridged tricyclic **11**, which was obtained in 73% yield from the cycloaddition of linker chain-extended allenyl oxazole **10**.

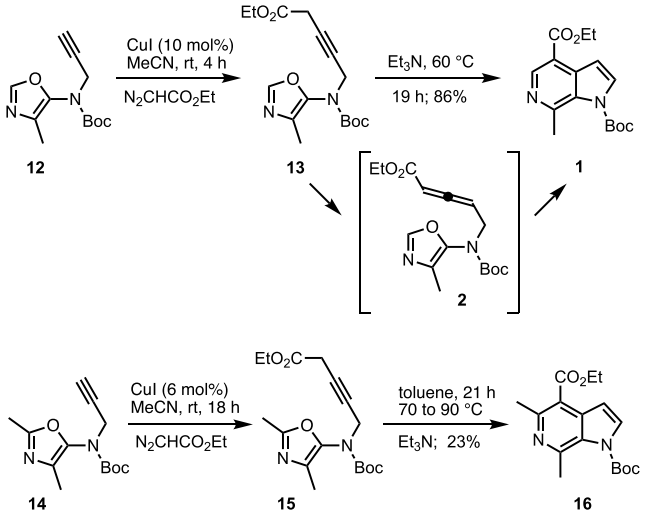
Scheme 3. Thermal Conversions of Allenyl Furans 3 to Indoles 4 and the Mechanism for the Intramolecular [4+2] Cycloadditions of Allenyl Oxazoles 6 and 10, Resulting in 6-Azaindole 7 and Bridged Tricycle 11



A convenient method for generating substituted 6-azaindoles presented itself in the alkyne−allene isomerization/*in situ* IMDAO reaction of esters **13** and **15** (Scheme 4). Copper(I)-catalyzed C,H-bond insertion of ethyl diazoacetate into alkyne **12** provided the internal alkyne **13**.[25,26] When **13** was gently heated in acetonitrile after addition of 2 equiv of triethylamine, isomerization[27] of the alkyne to allenoate **2** was followed by spontaneous IMDAO reaction and formation of 6-azaindole **1** in 86% overall yield from **12**. When the propargyl ester **15** was isolated after the Cu(I)-catalyzed ethyl diazoacetate insertion and the crude material was used for the cyclization in a solution in toluene, trisubstituted oxazole **14** was converted to 6-azaindole **16** in 23% overall yield. Possibly, the sharp drop in yield in the preparation of **1** versus **16** could be due to increased steric hindrance in the Diels−Alder transition state by the methyl group in position 2 of oxazole **15**. However, in contrast to the conversion of **12** to **1**, the preparation of other 6-azaindoles has not yet been fully optimized.

The successful and high-yielding preparation of 6-azaindole **1** set the stage for an application of this new synthetic method

Scheme 4. Preparation of Propargyl Ester Intermediates 13 and 15, Followed by Conversion to 6-Azaindoles 1 and 16 in a Tandem Alkyne−Allene Isomerization/IMDAO Sequence



in the total synthesis of marinoquinoline A, a marine metabolite that was first isolated in 2006 from the gliding bacterium *Rapidithrix thailandica* in a seaweed fraction collected at Yong Ling beach on the southern coast of Thailand.[28] Together with other structurally closely related C(2)-alkylated pyrroloquinoles, i.e., marinoquinolines B−F, marinoquinoline A was also identified in 2011 as a secondary metabolite of the gliding bacterium *Ohtaekwangia kribbensis*.[29] In 2015, marinoquinolines G−K were described in cultures of the marine bacterium *Mooreia alkaloidigena*.[30] In addition to a potent inhibitory effect on acetylcholine esterase[31] and weak antibacterial, antifungal, and cytotoxic properties,[29] the marinoquinolines also possess significant antimalarial activities and have served as lead structures for the development of fast-acting *Plasmodium falciparum* inhibitors.[29,32] Furthermore, related natural products, such as the ascidian metabolite aplidiopsamine A, are known to have central nervous system activities.[33]

The combination of a broad range of attractive biological properties and the presence of the unusual 3*H*-pyrrolo[2,3-*c*]quinoline core structure have attracted a great deal of attention to the synthesis of marinoquinolines,[34] including investigations of the biosynthetic gene clusters of these aminophenylpyrrole alkaloids (also known as APPAs).[35] After several preparations of the pyrroloquinoline core,[36] the first total synthesis of marinoquinoline A was accomplished by Yao and co-workers in 2012 by a TosMIC preparation of the pyrrole and a Morgan−Walls quinoline synthesis.[37] Shortly afterward, Banwell, Willis, and co-workers reported the use of a Pd(0)-catalyzed Ullmann cross-coupling of an iodo-pyrrole with 2-bromonitrobenzene followed by a reductive quinoline ring closure for the assembly of marinoquinoline A.[38] Also in 2012, Correia and Schwalm published a synthesis based on Heck−Matsuda and Pictet−Spengler reactions,[39] and Lindsley and Panarese used an analogous Suzuki coupling followed by a Bischler−Napieralski quinoline ring closure (Figure 1).[40] Mhaske and co-workers utilized a variation of this strategy by subjecting the imine of iodoaniline and 2-acetylpyrrole to a Pd-catalyzed bond formation and ring closure.[41] Another adaptation of this process was showcased in 2015 by Patel and

https://dx.doi.org/10.1021/acs.orglett.0c00417
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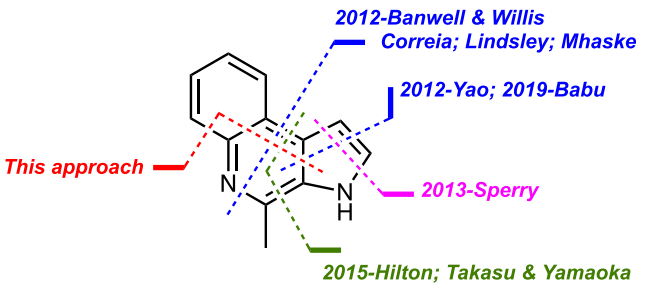


Figure 1. Key bond formations in prior marinoquinoline syntheses and approaches to the 3*H*-pyrrolo[2,3-*c*]quinoline core structure.

Hilton, who used the Togni trifluoromethylating reagent for the formation of a radical-mediated quinoline from a 2-pyrroloarylisocyanide.[42] Also in 2015, Takasu, Yamaoka, and coworkers formed the pyridine core of marinoquinoline A by an arene-ynamide cyclization involving a keteniminium ion intermediate.[43]

In 2013, Sperry and Lindsay prepared a 3*H*-pyrrolo[2,3-*c*]quinoline by a Bartoli indolization of 2-chloro-3-nitroquinoline in an approach toward marinoquinolines C and E that could be extended to marinoquinoline A.[44] Most recently, Babu and co-workers also generated the pyrroloquinoline core structure by insertion of TosMIC into 3-ylideneoxindoles.[45]

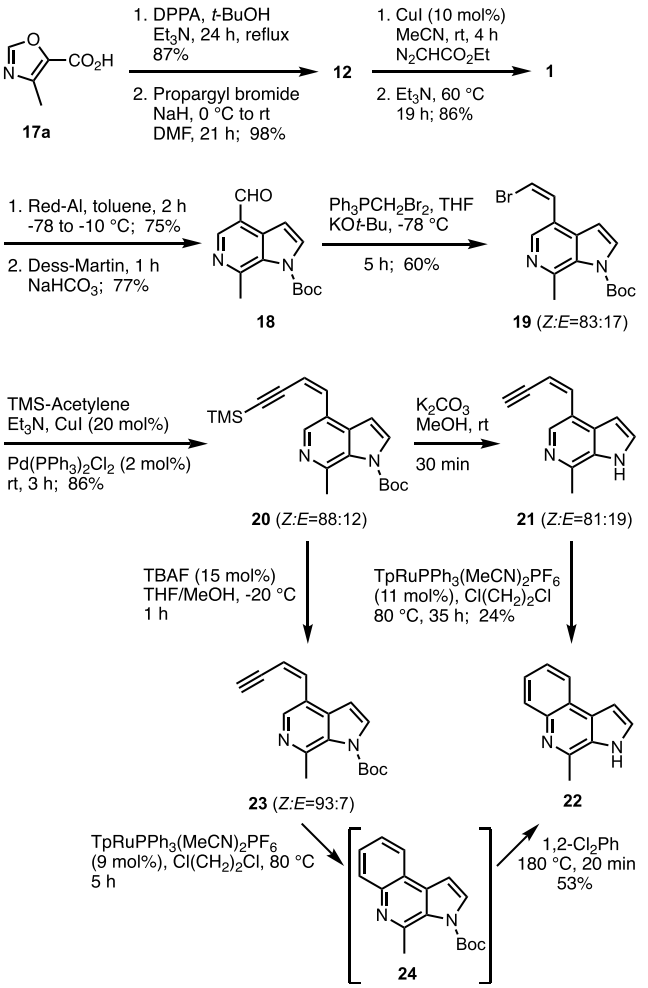
It is noteworthy that in spite of the wealth of approaches toward the marinoquinolines since 2012, the IMDAO approach still represents a unique and efficient retrosynthetic strategy to construct the pyrroloquinoline scaffold, in particular when coupled with an electrocyclic reaction to annulate the benzene ring (Scheme 1).

Starting with the commercially available oxazole acid **17a**, a Curtius rearrangement followed by N-alkylation with propargyl bromide provided alkyne **12** (Scheme 5). Cu(I)-catalyzed C,H-bond insertion into the terminal alkyne hydrogen and isomerization to the allenoate were followed by the spontaneous IMDAO reaction to provide **1** in 73% overall yield from **17a**. A two-step conversion was used to prepare the aldehyde **18**, because the DIBAL-H reduction as well as borohydride reagents cleaved the Boc group and gave a mixture of products, and only the Red-Al reduction with a low-temperature quench provided the intermediate primary alcohol in high yield. Oxidation of this alcohol with Dess−Martin periodinane provided **18** in 42% yield from **17a**. A Wittig reaction with bromomethylidene phosphorane gave the alkenyl bromide **19** in 60% yield as an 83:17 *Z* isomer/*E* isomer mixture. The subsequent Sonogashira reaction with TMS-acetylene was stereospecific and did not fundamentally change this ratio of inseparable alkene isomers.

While, initially, we proceeded with the removal of both TMS and Boc protective groups under mildly basic methanolysis conditions to give **21**, the subsequent ruthenium-catalyzed benzannulation[46] required prolonged heating in 1,2-dichloroethane and gave the desired target compound, marinoquinoline A (**22**), in a modest 24% overall yield from **20**. In contrast, sequential removal of TMS and Boc groups, with the latter deprotection as the last step of the synthesis, more than doubled the overall efficiency of the process.

Treatment of **20** with 15 mol % TBAF in a THF/methanol mixture at −20 °C for 1 h cleanly generated the Boc-protected 6-azaindole **23**, which was subjected to 9 mol % $TpRuPPh_3(MeCN)_2PF_6$ for 5 h at 80 °C. It was important to filter the crude solution of **23** through a plug of neutral Al_2O_3 before the electrocyclization reaction, because traces of TBAF inhibited the catalyst in the benzannulation. Without further purification, the filtered solution of Boc-protected marinoquinoline **24** was then added to 1,2-dichlorobenzene in a microwave reaction vial, and brief heating at 180 °C cleaved[47] the Boc group to generate marinoquinoline A (**22**) in 53% overall yield from intermediate **20**. Control reactions with batches of **20** that were highly enriched in the (*E*)-alkene isomer confirmed that only the (*Z*)-alkene underwent the desired benzannulation.

Scheme 5. Total Synthesis of Marinoquinoline A



In summary, we were able to extend the formation of indoles by the IMDAF of allenes to the analogous oxazole series, which yielded synthetically useful[48] 6-azaindole building blocks. The IMDAO reaction provided the foundation for a unique retrosynthetic design to the pyrroloquinoline marinoquinoline A. The target marine natural product **22** was obtained in 12% overall yield from commercially available oxazole **17a**, and in addition to the IMDAO reaction, the total synthesis also featured the use of a propargylic C,H-bond insertion, an *in situ* alkyne-allene isomerization, and a ruthenium-catalyzed benzannulation. Beyond showcasing a novel synthetic strategy, this approach should readily lend itself to the preparation of new pyrroloquinolines for future investigations of their broad biological properties.

https://dx.doi.org/10.1021/acs.orglett.0c00417
Org. Lett. XXXX, XXX, XXX−XXX

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00417.

Experimental details and ^{1}H and ^{13}C NMR spectra for new synthetic intermediates and products (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Peter Wipf − *Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, United States;* orcid.org/0000-0001-7693-5863; Email: pwipf@pitt.edu

Authors

Mana Osano − *Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, United States; Department of Applied Chemistry, School of Science and Technology, Meiji University, Kawasaki 214-8571, Japan*

Dishit P. Jhaveri − *Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c00417

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank T. Maskrey and D. Crocker for significant help in the preparation of the manuscript and Supporting Information and also acknowledge Boehringer-Ingelheim Pharmaceuticals (Ridgefield, CT) for discretionary funding supporting this research. M.O. is a grantee of the Japan Student Services Organization (JASSO) Japan Public-Private Partnership Student Study Abroad Program (TOBITATE! Young Ambassador Program).

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