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Issue 14; July 2017

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Recent Publications of ISHC Members

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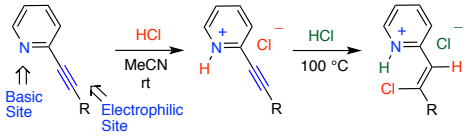
Hydrohalogenation of Ethynylpyridines Involving Nucleophilic Attack of a Halide Ion

Kengo Muragishi, Haruyasu Asahara, and Nagatoshi Nishiwaki

ACS Omega **2017**, *2*, 1265–1272. **DOI:** 10.1021/acsomega.7b00133

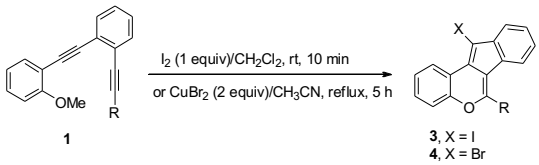


Abstract: Efficient hydrochlorination of 2-ethynylpyridines was achieved without the use of special reagents. Ethynylpyridine readily reacts with hydrochloric acid to form a pyridinium salt. The salt formation considerably enhances the electrophilicity of the ethynyl group and attracts a chloride ion as the counteranion. The spatial proximity facilitates the nucleophilic addition of the halide anion to the ethynyl group, producing 2-(2-chloroethenyl)pyridine in high yields. This protocol could also be applied for hydrobromination and hydroiodination using hydrobromic and hydroiodic acids, respectively. In the case of acetic acid, the reaction did not proceed because of the low acidity and lack of salt formation. This problem was overcome by exchanging the counteranion using silver acetate; the resultant pyridinium acetate underwent hydroacetoxylation.

Halogen-Mediated Cascade Cyclization Reaction of Aryldiynes to Indeno[1,2-*c*]chromene Derivatives

Chin-Chau Chen, Man-Yun Wu, Hsing-Yin Chen, and Ming-Jung Wu

J. Org. Chem. **2017**, *82*, 6071–6081. **DOI:** 10.1021/acs.joc.7b00538

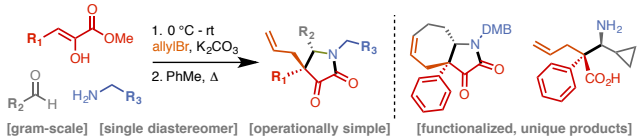


Abstract: The halogen-mediated cyclization reaction of aryldiynes to produce halogenated indeno[1,2-*c*]chromene derivatives is described. Treatment of aryldiynes **1** with one equivalent of iodine gave iodinated indeno[1,2-*c*]chromenes **3** in good chemical yields. When two equivalents of iodine were employed into the reaction mixture, dimer **9** was obtained as the major products. On the other hand, reaction of two equivalents of $CuBr_2$ with compounds **1** gave the brominated indeno[1,2-*c*]chromenes **4**. The DFT calculation of the iodine-mediated cyclization reactions for molecules containing methoxy, carboxy, amino, and sulfide substituents were carried out in order to understand how the substituent affects the cyclization pathway.

Stereoselective Synthesis of Quaternary Pyrrolidine-2,3-diones and β-Amino Acids

Nataliia V. Shymanska and Joshua G. Pierce

Org. Lett. **2017**, *19*, 2961–2964. **DOI:** 10.1021/acs.orglett.7b01185



Abstract: A facile, diastereoselective synthesis of highly substituted pyrrolidine-2,3-diones is reported, along with the one-step conversion of these heterocycles to novel β-amino acids and further functionalized derivatives. This method involves an unusually mild, one-pot, three-component cyclization/allylation followed by a Claisen rearrangement to provide unusual pyrrolidinone products that are densely functionalized and contain an all-carbon quaternary stereocenter. The reported reaction sequence is operationally simple, exquisitely diastereoselective, and provides gram-scale access to valuable heterocyclic scaffolds and β-amino acids not readily accessible via existing approaches.

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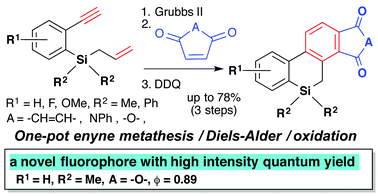
One-pot Enyne Metathesis/Diels–/Alder/Oxidation to Six-Membered Silacycles with a Multi-ring Core: Discovery of Novel Fluorophores

Shohei Yoshioka, Yuki Fujii, Hirofumi Tsujino, Tadayuki Uno, Hiromichi Fujioka, and Mitsuhiro Arisawa

Chem. Commun. **2017**, *53*, 5970–5973. **DOI:** 10.1039/c7cc02788e

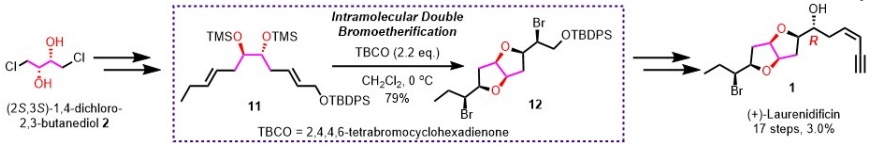


Abstract: Polycyclic compounds containing a six-membered silacycle are important. However, we have limited knowledge of the nature of these six-membered silacycles because methodologies for their synthesis remain under-developed. Here, we have developed a one-pot enyne metathesis/Diels–Alder/oxidation methodology for the synthesis of six-membered silacycles. Some of these compounds are novel fluorophores.

First Asymmetric Total Synthesis and Insight into the Structure of Laurenidificin

Yusuke Yoshikawa, Maki Yamakawa, Tetsuya Kobayashi, Kenichi Murai, Mitsuhiro Arisawa, Michinori Sumimoto, and Hiromichi Fujioka

Eur. J. Org. Chem. **2017**, 2715–2718. **DOI:** 10.1002/ejoc.201700321

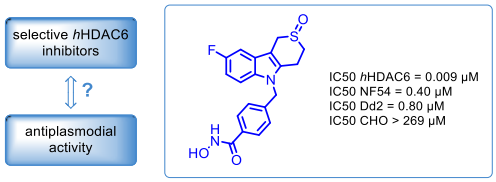


Abstract: (+)-Laurenidificin has a fused bis-THF skeleton and an enyne structure in its side chain. It is known that the bis-THF skeleton is *cis*,*cis* fused, and the absolute configuration at the C6 position is *R*, but the whole structure has not been determined. We synthesized one possible isomer of (+)-laurenidificin by using intramolecular double bromoetherification as a key step. Treatment of a protected (*E*,*E*)-diene diol with 2,4,4,6-tetrabromo-2,5-cyclohexadienone as the halogenating agent afforded a *cis*,*cis*-fused bis-THF derivative in good yield with high stereoselectivity. Several additional transformations, including introduction of a hydroxy group at the C6 position and construction of the enyne structure, gave a possible isomer of (+)-laurenidificin. The ^{1}H NMR and ^{13}C NMR spectroscopy data of this isomer are in complete agreement with those of natural (+)-laurenidificin, and its optical rotation and that of natural laurenidificin have the same positive sign.

Exploration of Thiaheterocyclic *h*HDAC6 Inhibitors as Potential Antiplasmodial Agents

Rob De Vreese, Carmen de Kock, Peter J. Smith, Kelly Chibale, and Matthias D'hooghe

Future Med. Chem. **2017**, *9*, 357–364. **DOI:** 10.4155/fmc-2016-0215

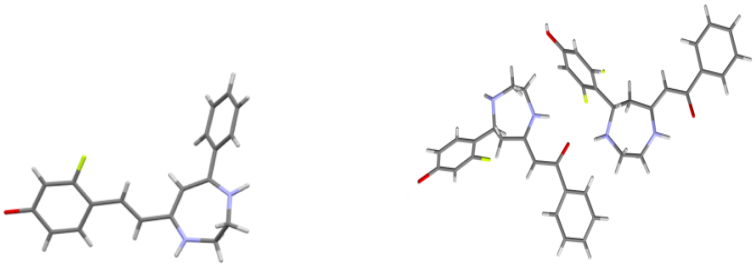


Abstract: The recurring resistance of the malaria parasite to many drugs compels the design of innovative chemical entities in antimalarial research. Pan-histone deacetylase inhibitors (pan-HDACi's) have recently been presented in the literature as powerful novel antimalarials, although their application is hampered due to toxic side effects. This drawback might be neutralized by the deployment of isoform-selective HDAC inhibitors. In this study, 42 thiaheterocyclic benzohydroxamic acids, 17 of them being potent and selective *h*HDAC6 inhibitors, were tested to investigate a possible correlation between *h*HDAC6 inhibition and antiplasmodial activity. Four *h*HDAC6 inhibitors showed submicromolar potency against both a chloroquine-sensitive and a chloroquine-resistant strain of *Plasmodium falciparum* with high Selectivity Indices, pointing to the relevance of exploring *h*HDAC6 inhibitors as potential new antiplasmodial agents.

Curcumin Related 1,4-Diazepines: Regioselective Synthesis, Structure Analysis, Tautomerism, NMR Spectroscopy, X-ray Crystallography, Density Functional Theory and GIAO Calculations

Carla I. Nieto, Ana Andrade, Dionisia Sanz, Rosa M. Claramunt, M. Carmen Torralba, M. Rosario Torres, Ibon Alkorta, and José Elguerdo

ChemistrySelect **2017**, *2*, 3732–3738. **DOI:** 10.1002/slct.201700405



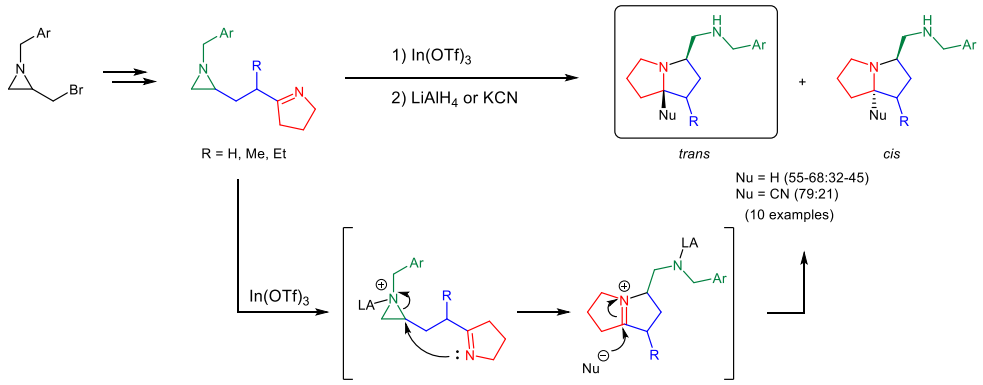
1d **2d**

Abstract: Reaction of 1,2-ethylenediamine with seven fluorinated β-diketones affords two series of 1,4-diazepines **1** and **2** whose structures have been established by NMR together with Density Functional Theory calculations. In the case of the **d** derivatives (2′-fluoro-4′-hydroxy) X-ray crystal analysis and solid-state NMR was also applied.

Concise Synthesis of 3-(Aminomethyl)pyrrolizidines via an $In(OTf)_3$-Mediated Ring Rearrangement of 2-[2-(1-Pyrrolin-2-yl)-alkyl]aziridines

Jeroen Dolfen and Matthias D'hooghe

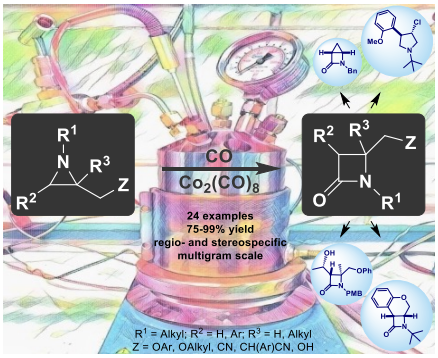
Synthesis **2017**, *49*, 2215–2222. **DOI:** 10.1055/s-0036-1588404



Abstract: In this study, an efficient ring rearrangement of 2-[2-(1-pyrrolin-2-yl)alkyl]aziridines, prepared from 2-(bromomethyl)aziridines, toward novel *trans* and *cis* 3-aminomethyl-substituted pyrrolizidines was developed. To that end, addition of $In(OTf)_3$ as an appropriate Lewis acid catalyst resulted in the formation of intermediate pyrrolizidinium salts *via* regioselective aziridine ring opening, which were then trapped by a hydride or cyanide nucleophile. Column chromatographic purification allowed the isolation of the major *trans* isomers, exclusively.

Cobalt Carbonyl-Catalyzed Carbonylation of Functionalized Aziridines to Versatile β-Lactam Building Blocks

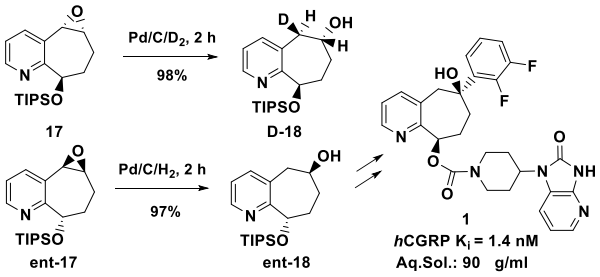
Nicola Piens, Kristof Van Hecke, Dieter Vogt, and Matthias D'hooghe
Org. Biomol. Chem. **2017**, *15*, 4816–4821. **DOI:** 10.1039/c7Ob00832e



Abstract: $Co_2(CO)_8$-catalyzed carbonylation of different classes of non-activated aziridines with diverse substitution patterns was investigated. Special attention was devoted to selectivity issues and reaction optimization. This study resulted in the regio- and stereospecific synthesis of 24 novel β-lactam target structures in high yields on a multigram scale. The synthetic potential of the newly obtained azetidin-2-ones was illustrated *via* ring-expansion, ring-closure, and/or side chain-functionalization protocols to provide a straightforward entry to novel pyrrolidines, *C*-fused bi- and tricyclic β-lactams and monocyclic carbapenem analogs.

Asymmetric Synthesis of the Major Metabolite of a Calcitonin Gene-Related Peptide Receptor Antagonist and Mechanism of Epoxide Hydrogenolysis

Guanglin Luo, Ling Chen, Charles M. Conway, Walter Kostich, Benjamin M. Johnson, Alicia Ng, John E. Macor, and Gene M. Dubowchik
J. Org. Chem. **2017**, *82*, 3710–3720. **DOI:** 10.1021/acs.joc.7b00052



Abstract: An asymmetric synthesis of the major metabolite of the calcitonin gene-related peptide recepotor antagonist BMS-846372 is presented. The variously substituted cyclohepta[*b*]pyridine ring system represents an underexplored ring system and showed some unexpected chemistry. Reactivities of epoxide and ketone functional groups on the cycloheptane ring were extensively controlled by a remote bulky TIPS group. The rate difference of the hydrogenolysis between two diastereomeric epoxide intermediates shed some light on the mechanism of epoxide hydrogenolysis, and further, deuterium labeling studies revealed more mechanistic details on this well-known chemical transformation for the first time.