Issue 19; April 2018

The ISHC Bulletin

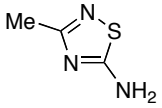
Recent Publications of ISHC Members

Issue 19; April 2018

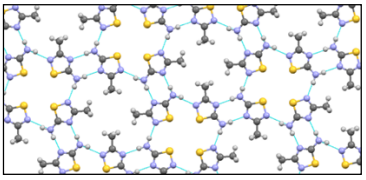
5-Amino-3-methyl-1,2,4-thiadiazole

R. Alan Aitken and Alexandra M. Z. Slawin

Molbank **2018**, *2018*, M977 (1–5). **DOI:** 10.3390/M977



prepared on multi-gram scale
^{1}H, ^{13}C NMR, IR, X-ray structure

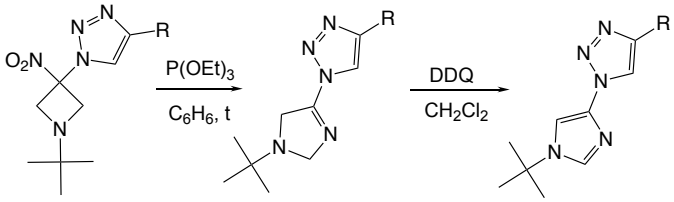


Abstract: An improved procedure for isolation of 5-amino-3-methyl-1,2,4-thiadiazole in pure form on a multi-gram scale without chromatography is reported. Its ^{1}H and ^{13}C-NMR and IR data are presented and previously published erroneous data corrected. The molecular structure is confirmed by X-ray diffraction which shows layers consisting of an elaborate two-dimensional hydrogen bonded network of molecules.

A New Method of Synthesis of Substituted 1-(1*H*-Imidazole-4-yl)-1*H*-1,2,3-triazoles and Their Fungicidal Activity

Mikhail V. Dubovis, Gennady F. Rudakov, Alexander S. Kulagin, Kseniya V. Tsarkova, Sergey V. Popkov, Alexander S. Goloveshkin, Georgiy V. Cherkaev

Tetrahedron **2018**, *74*, 672–683. **DOI:** 10.1016/j.tet.2017.12.043



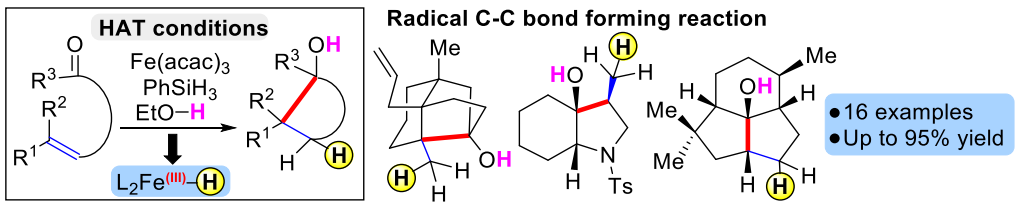
11 examples

Abstract: Based on the deoxygenation reaction of 1-(1-*tert*-butyl-3-nitroazetidine-3-yl)-1*H*-1,2,3-triazoles a new method for the synthesis of substituted 1-(1*H*-imadazole-4-yl)-1*H*-1,2,3-triazoles has been developed. Fungicidal activity of these compounds has been investigated at a range of phytopathogenic fungi.

Radical Cyclization of Alkene-Tethered Ketones Initiated by Hydrogen-Atom Transfer

Mar Saladrigas, Caroline Bosch, Gisela V. Saborit, Josep Bonjoch, Ben Bradshaw

Angew. Chem. Int. Ed. **2018**, *57*, 182–186. **DOI:** 10.1002/anie.201709659



Abstract: An unprecedented C–C coupling reaction between alkenes and ketones by hydrogen-atom transfer, using $Fe(acac)_3$ and $PhSiH_3$ in EtOH, is described. This mild protocol features high site selectivity and allows the construction of sterically congested structures containing tertiary alcohols and quaternary centers. The overall process introduces a novel strategic bond disconnection for ring-closing reactions.

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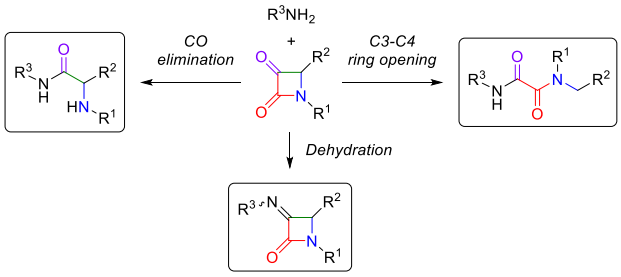
Reactivity of 3-Oxo-β-lactams with Respect to Primary Amines – An Experimental and Computational Approach

Nicola Piens, Hannelore Goossens, Dietmar Hertsen, Sari Deketelaere, Lieselotte Crul, Lotte Demeurisse, Jelle De Moor, Elias Van den Broeck, Karen Mollet, Kristof Van Hecke, Veronique Van Speybroeck, Matthias D'hooghe

Chem. Eur. J. **2017**, *23*, 18002–18009. **DOI:** 10.1002/chem.201703852

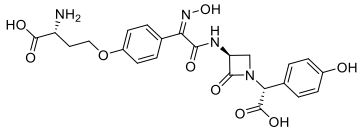


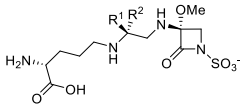
Abstract: The reactivity of 3-oxo-β-lactams with respect to primary amines was investigated in depth. Depending on the specific azetidin-2-one C4 substituent, this reaction was shown to selectively produce 3-imino-β-lactams (through dehydration), α-aminoamides (through CO elimination) or ethanediamides (through an unprecedented C3-C4 ring opening). In addition to the experimental results, the mechanisms and factors governing these peculiar transformations were also examined and elucidated by means of density functional theory calculations.

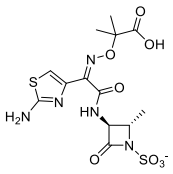
Antibacterial and β-Lactamase Inhibitory Activity of Monocyclic β-Lactams

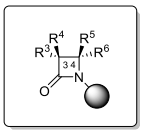
Lena Decuyper, Marko Jukič, Izidor Sosič, Aleš Žula, Matthias D'hooghe, Stanislav Gobec

Med. Res. Rev. **2018**, *38*, 426–503. **DOI:** 10.1002/med.21443


Nocardicin A


Sulfazecin (R^1 = H, R^2 = Me) and isosulfazecin (R^1 = Me, R^2 = H)


Aztreonam

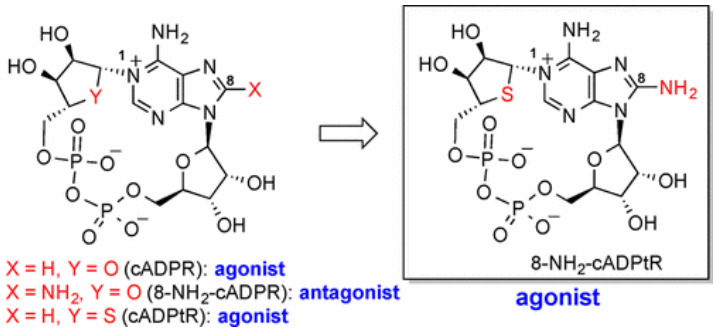


Abstract: Due to the widespread emergence of resistant bacterial strains, an urgent need for the development of new antibacterial agents with novel modes of action has emerged. The discovery of naturally occurring monocyclic β-lactams in the late 1970s, mainly active against aerobic Gram-negative bacteria, has introduced a new approach in the design and development of novel antibacterial β-lactam agents. The main goal was the derivatization of the azetidin-2-one core in order to improve their antibacterial potency, broaden their spectrum of activity and enhance their β-lactamase stability. In that respect, our review covers the updates in the field of monocyclic β-lactam antibiotics during the last three decades, taking into account an extensive collection of references. An overview of the relationships between the structural features of these monocyclic β-lactams, classified according to their *N*-substituent, and the associated antibacterial or β-lactamase inhibitory activities is provided. The different paragraphs disclose a number of well-established classes of compounds, such as monobactams, monosulfactams, monocarbams, monophosphams, nocardicins, as well as other known representative classes. Moreover, this review draws attention to some less common but, nevertheless, possibly important types of monocyclic β-lactams, and concludes by highlighting the recent developments on siderophore-conjugated classes of monocyclic β-lactams.

Synthesis of 8-Substituted Analogues of Cyclic ADP-4-Thioribose and Their Unexpected Identification as Ca^{2+}-Mobilizing Full Agonists

Satoshi Takano, Takayoshi Tsuzuki, Takashi Murayama, Tomoshi Kameda, Yasuhiro Kumaki, Takashi Sakurai, Hayato Fukuda, Mizuki Watanabe, Mitsuhiro Arisawa, Satoshi Shuto

J. Med. Chem. **2017**, *60*, 5868–5875. **DOI:** 10.1021/acs.jmedchem.7b00540

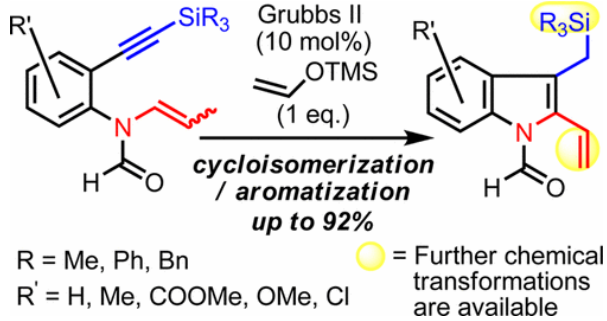


Abstract: A series of 8-substituted analogues of cyclic ADP-4-thioribose (cADPtR, **3**), which is a stable equivalent of Ca^{2+}-mobilizing second messenger cyclic ADP-ribose (cADPR, **1**), were designed as potential pharmacological tools for studies on cADPR-modulated Ca^{2+} signaling pathways. These 8-amino analogue (8-NH_2-cADPtR, **4**), 8-azido analogue (8-N_3-cADPtR, **5**), and 8-chloro analogue (8-Cl-cADPtR, **6**) were efficiently synthesized, where the stereoselective *N*1-β-thioribosyladenine ring closure reaction via an α/β-equilibrium of the 1-aminothioribose derivative and construction of the characteristic 18-membered pyrophosphate ring by Ag^{+}-promoted activation of a phenyl phosphorothioate type substrate were the two key steps. Although 8-NH_2-cADPR (**2**) is a well-known potent antagonist against cADPR-inducing Ca^{2+}-release, the 4-thioribose congener 8-NH_2-cADPtR turned out unexpectedly to be a full agonist in sea urchin egg homogenate evaluation system. This important finding suggested that the ring-oxygen in the *N*1-ribose of cADPR analogues is essential for the antagonistic activity in the Ca^{2+}-signaling pathway, which can contribute to clarify the structure–agonist/antagonist activity relationship.

Ruthenium-Catalyzed 1,6-Aromatic Enamide–Silylalkyne Cycloisomerization: Approach to 2,3-Disubstituted Indoles

Kohei Takamoto, Shohei Ohno, Norimichi Hyogo, Hiromichi Fujioka, Mitsuhiro Arisawa

J. Org. Chem. **2017**, *82*, 8733–8742. **DOI:** 10.1021/acs.joc.7b01288

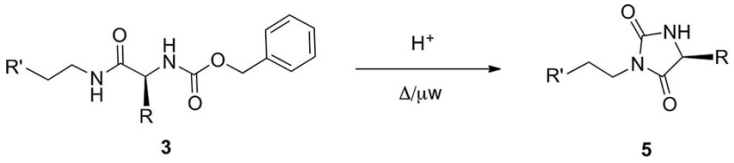


Abstract: Cycloisomerization is an atom economic procedure that converts dienes and enynes into cyclic molecules. To date, cycloisomerization between enamides and silylalkynes has not been explored. We found that *N*-acyl-*N*-vinyl-2-silylalkynylaniline derivatives undergo a cycloisomerization in the presence of a well-defined ruthenium hydride to give a 2,3-disubstitued indole. The vinyl and silylmethyl substituents on the 2- and 3-positions of the indole can be easily converted to other functional groups.

Thermolysis Reactions of *N*-Alkyl-*N'*-CBZ Amino Acid Amides. A Route to Substituted Imidazolidine-2,4-diones

Marc Casale and David A. Hunt

Tetrahedron Lett. **2018**, *59*, 938–940. **DOI:** 10.1016/j.tetlet.2018.01.086

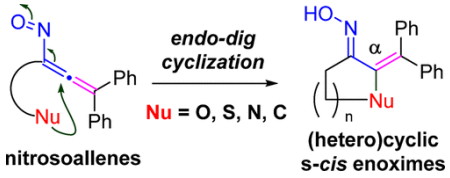


Abstract: Reaction of *N*-alkyl-*N'*-CBZ amino acid amides under microwave conditions in water and in the presence of an acid catalyst results in the formation of *N*-substituted imidazolidine-2,4-diones in good yields.

Nitrosoallene-Mediated *endo*-Cyclizations for the Synthesis of (Hetero)cyclic α-Substituted *exo*-Unsaturated Oximes

Hiroki Tanimoto, Sho Ueda, Tsumoru Morimoto, Kiyomi Kakiuchi

J. Org. Chem. **2018**, *83*, 1614–1626. **DOI:** 10.1021/acs.joc.7b02936

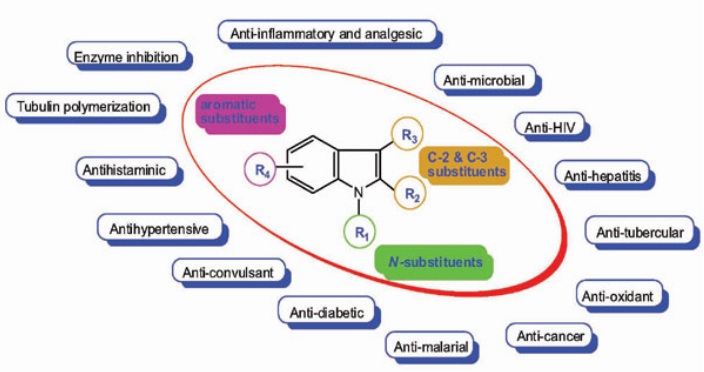


Abstract: Nitrosoallene-mediated *endo*-dig cyclization reactions producing (hetero)cyclic *exo*-unsaturated oximes (enoximes) are described. The intramolecular 1,4-type addition to *in situ* generated nitrosoallenes afforded α-substituted cyclic enoximes with *exo*-methylene units, which are the favored conformation for futher cyclizations. The strong electron-withdrawing ability of the nitroso group facilitated the construction of five-to-seven-membered ring systems via C–O, C–N, C–S, and C–C bond formations, including a quaternary carbon center, at low temperatures.

Recent Progress in Biological Activities of Indole and Indole Alkaloids

Thokchom P. Singh and Okram M. Singh

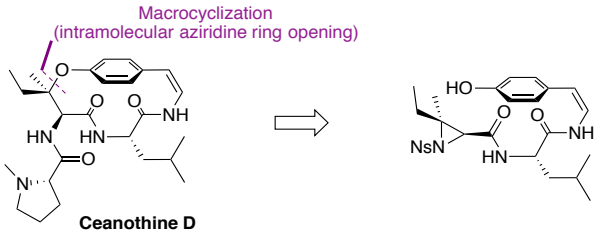
Mini-Rev. Med. Chem. **2018**, *18*, 9–25. **DOI:** 10.2174/1389557517666170807123201



Abstract: The indole scaffold is found in a wide range of bioactive heterocycles and natural products. Moreover, the indole moiety is considered as the active principle in several alkaloids such as mitomycin C and reserpine. Thus, over the past decade, chemists are increasingly attracted towards the studies on the pharmacological and therapeutic activities of indole containing compounds. Furthermore, the molecular structures of well-known drugs such as sumatriptan, tadalafil, fluvastatin and rizatriptan are based on indole frameworks. This mini-review covers some of the significant and recent achievements of indole derivatives with respect to their biological activities up to 2015.

Total Synthesis of the Reported Structure of Ceanothine D *via* a Novel Macrocyclization Strategy

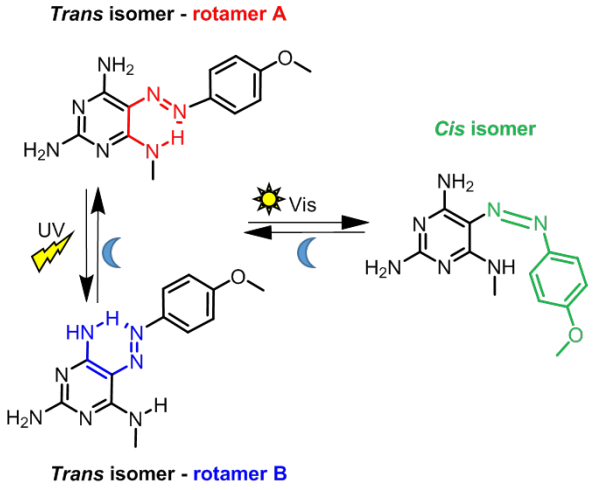
Jisun Lee and Madeleine M. Joullié
Chem. Sci. **2018**, *9*, 2432–2436. **DOI:** 10.1039/c8sc00234g



Abstract: The first total synthesis of the reported structure of ceanothine D, a cyclopeptide alkaloid found in red root, was achieved using a highly convergent synthetic strategy. Highlights of the synthesis include the first concomitant macrocyclization and formation of the unique chiral tertiary alkyl-aryl ether bond with a complete regio- and stereocontrol in the presence of a sensitive *Z*-enamide moiety to access the strained para-cyclophane present in its structure. This synthetic strategy may be broadly applicable in the generation of other structurally similar cyclopeptide alkaloids, enabling further biological and chemical investigations.

Photoswitchable Intramolecular Hydrogen Bonds in 5-Phenylazopyrimidines Revealed by *in situ* Irradiation NMR Spectroscopy

Eliška Procházková, Lucie Čechová, Jonas Kind, Zlatko Janeba, Christina M. Thiele, Martin Dračínský
Chem. Eur. J. **2018**, *24*, 492–498. **DOI:** 10.1002/chem.201705146



Abstract: NMR spectroscopy with *in situ* irradiation uncovered unique photoswitchable intramolecular hydrogen bonds (IMHBs) in 5-phenylazopyrimidines with two hydrogen bond donors. These compounds form two stable rotamers, each with one IMHB, and the rotamer ratio changes reversibly upon UV or visible light irradiation. Strong substituent dependence of photoinduced structural changes was observed; using suitable substituents, orthogonal photoswitching can be achieved. For example, whereas UV irradiation caused switching between the two rotamers of the trans isomer of a compound with electron-donating methoxy substituent, visible light enabled to obtain the cis photoisomer. No cis isomer was detected for compounds with electro-neutral or electron-accepting substituents, but photoswitching between the two trans isomers was observed. On the other hand, compounds without hydrogen-bond donors or with one donor only formed stable cis isomers. A mechanism of the photoswitching was proposed by DFT computations.