

The ISHC Bulletin

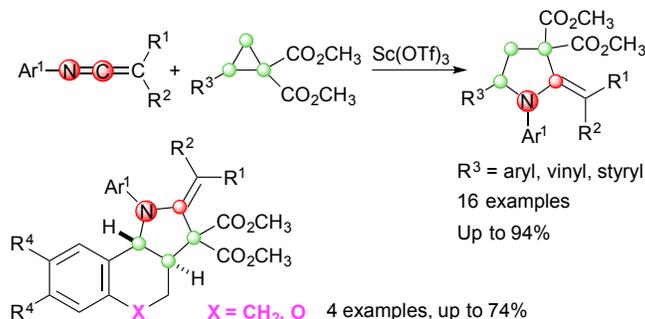
Recent Publications of ISHC Members

Issue 8; January 2017

Lewis Acid Catalyzed [3 + 2] Annulation of Ketenimines with Donor-Acceptor Cyclopropanes: An Approach to 2-Alkylidenepyrrolidine Derivatives

Mateo Alajarin, Adrian Egea, Raul-Angel Orenes and Angel Vidal
Org. Biomol. Chem. **2016**, *14*, 10275–10284.

DOI: 10.1039/c6ob02005d

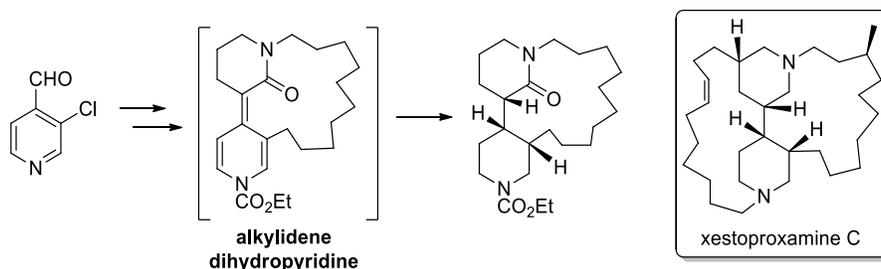


Abstract: The [3 + 2] annulation reaction of *C,C,N*-trisubstituted ketenimines with donor–acceptor cyclopropanes bearing aryl, styryl and vinyl substituents at the C2 position, triggered by the Lewis acid Sc(OTf)₃, supplies highly substituted pyrrolidines. Activated cyclopropanes fused to naphthalene and [1]benzopyrane nuclei are also suitable substrates in similar transformations, yielding partially saturated benz[*g*]indoles and [1]benzopyran[4,3-*b*]pyrroles. An intramolecular version of this ketenimine/cyclopropane [3 + 2] annulation has also been developed leading to the pyrrolo[2,1-*a*]isoindole framework.

Alkylidene Dihydropyridines As Synthetic Intermediates: Model Studies toward the Synthesis of the Bis(piperidine) Alkaloid Xestoproxamine C

Ashabha I. Lansakara, S. V. Santhana Mariappan and F. Christopher Pigge
J. Org. Chem. **2016**, *81*, 10266–10278.*

DOI: 10.1021/acs.joc.6b01269



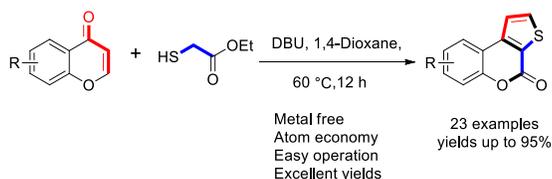
Abstract: Results of model studies demonstrating a stereoselective synthetic route to tricyclic analogues of the bis(piperidine) alkaloid xestoproxamine C are presented. Dearomatization of a tricyclic pyridine derivative to afford an alkylidene dihydropyridine (anhydrobase) intermediate followed by catalytic heterogeneous hydrogenation was used to install the correct relative stereochemistry about the bis(piperidine) ring system. Other key features of these model studies include development of an efficient ring-closing metathesis procedure to prepare macrocyclic derivatives of 3,4-disubstituted pyridines, intramolecular cyclizations of alkylidene dihydropyridines to establish pyridine-substituted pyrrolidines and piperidines, successful homologation of pyridine-4-carboxaldehydes using formaldehyde dimethyl thioacetal monoxide (FAMSO), and application of B-alkyl Suzuki coupling to assemble substituted pyridines.

*Special Issue dedicated to Heterocyclic Chemistry

One-Pot Transition-Metal-Free Cascade Synthesis of Thieno[2,3-*c*]coumarins from Chromones

Yuhong Yang, Xueyu Qi, Ruiling Liu, Qian He and Chunhao Yang
RSC Adv. **2016**, *6*, 103895–103898.

DOI: 10.1039/C6RA21776A

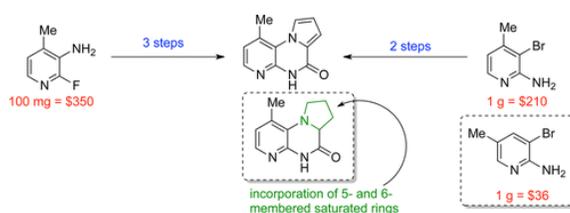


Abstract: A one-pot transition-metal-free, base-mediated synthesis of a novel series of functionalized thieno[2,3-*c*]coumarins via a cascade reaction from chromones has been developed. This cascade reaction involves a Michael addition-Knoevenagel Condensation-intramolecular cyclization. This transformation proceeds under mild conditions and gives various thieno[2,3-*c*]coumarins in good-to-excellent yields. The methodology is tolerant of a wide range of functional groups and applicable to library synthesis.

Synthesis of Kappa Opioid Antagonists Based On Pyrrolo[1,2- α]quinoxalinones Using an *N*-Arylation/Condensation/Oxidation Reaction Sequence

Sarah M. Scarry, Kimberly M. Lovell, Kevin J. Frankowski, Laura M. Bohn and Jeffrey Aubé
J. Org. Chem. **2016**, *81*, 10538–10550.*

DOI: 10.1021/acs.joc.6b01350

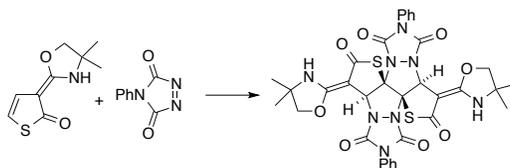


Abstract: The quinoxaline and quinoxalinone family of nitrogen heterocycles is present in molecules of therapeutic relevance for diverse applications ranging from infectious diseases to neuroscience targets. Here, we describe a general synthetic sequence to afford pyrrolo[1,2- α]quinoxalinones from commercially available starting materials and their use in preparing potential kappa opioid receptor antagonists. The biological data obtained from the latter set of compounds is briefly presented and discussed.

Synthesis, Structure and Unusual Reactivity of a Stable 3-(Oxazolidin-2-ylidene)thiophen-2-one

R. Alan Aitken, Andrew D. Harper and Alexandra M. Z. Slawin
J. Org. Chem. **2016**, *81*, 10527–10531.*

DOI: 10.1021/acs.joc.6b01309



Abstract: Treatment of 2- and 3-thienyloxazolidines with butyllithium and bis(trimethylsilyl) peroxide results in ring hydroxylation to give products which exist mainly as the oxazolidinylidenethiophenones. The 3-oxazolidinylidenethiophen-2-one is a rare example of a stable heterocyclic *ortho*-quinone methide analog which shows a varied pattern of reactivity, including both *C*- and *O*-alkylation, Michael addition via *C*-5 to an acetylenic ester, tetrachlorobenzannulation across positions 4 and 5, and formation of a hexacyclic fused-ring product with *N*-phenyltriazolinedione. Crystal structures of the products are dominated by inter and intramolecular NH to CO hydrogen bonding.

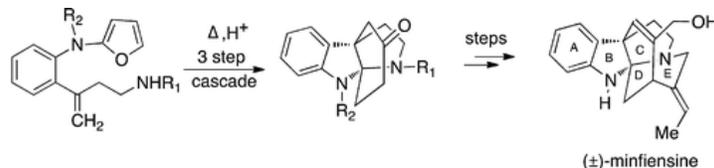
*Special Issue dedicated to Heterocyclic Chemistry

IMDAF Cascade Approach Toward the Synthesis of the Alkaloid (±)-Minfiensine

Carolyn A. Leverett, Gang Li, Stefan France and Albert Padwa

J. Org. Chem. **2016**, *81*, 10193–10203.*

DOI: 10.1021/acs.joc.6b00771



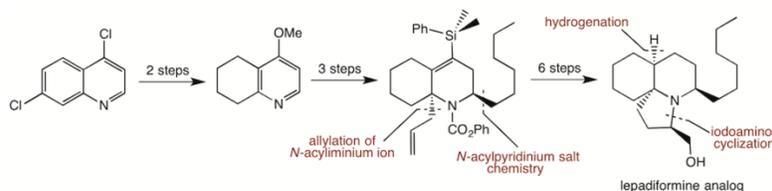
Abstract: The total synthesis of the *Strychnos* alkaloid (±)-minfiensine was achieved via an intramolecular amidofuran Diels-Alder (IMDAF) cycloaddition/ rearrangement followed by an iminium ion/cyclization cascade sequence. This domino process provides for a rapid access to the unique 1,2,3,4-tetrahydro-9a,4a- iminoethano-carbazole core structure found in the alkaloid minfiensine. In this paper the full account of our synthetic study is described, highlighting the successful application of the cascade sequence to form the A/B/C/D rings of (±)- minfiensine in high yield. A palladium-catalyzed enolate coupling reaction was then used to furnish the final E ring and complete the total synthesis of (±)- minfiensine.

Studies toward the Synthesis of Lepadiformine A

Sergey V. Tsukanov, Lucas R. Marks and Daniel L. Comins

J. Org. Chem. **2016**, *81*, 10433–10443.*

DOI: 10.1021/acs.joc.6b01514



Abstract: An original approach to access a tricyclic framework of the lepadiformine-type alkaloids is described. A Grignard/*N*-acylpyridinium salt reaction of a 4-methoxy tetrahydroquinoline was a key carbon-carbon bond-forming step that was used to establish the desired absolute stereochemistry at the C2 position of the target alkaloid. The synthesis features an allylation reaction with an *N*-acyliminium ion to set the C10 quaternary stereocenter, a mild dissolving-metal cleavage of hindered phenyl carbamates, and an improved aminoiodocyclization to form the pyrrolidine ring. While this route does not provide the correct C10 stereochemistry, it showcases an efficient method to build analogs with the ring system of this class of alkaloids in 11 steps overall.

Construction of 1,2,4-Triazole Derivatives via Cyclocondensation of Alkylidene Dihydropyridines and Aryldiazonium Salts

Madhur S. Joshi and F. Christopher Pigge

Org. Lett. **2016**, *18*, 5916–5919.

DOI: 10.1021/acs.orglett.6b03019



Abstract: Alkylidene dihydropyridines (anhydrobases) prepared via dearomatization of *N*-acylated 4-aminomethylpyridines participate in [3+2] cyclocondensation reactions with aryl diazonium cations to afford substituted 1,2,4-triazolium salts or neutral 1,2,4-triazoles in high isolated yield. The reaction proceeds in the presence of a variety of *N*-acyl groups and aryl-substituted diazonium salts, and offers a general route to pyridyl-substituted 1,2,4-triazoles.

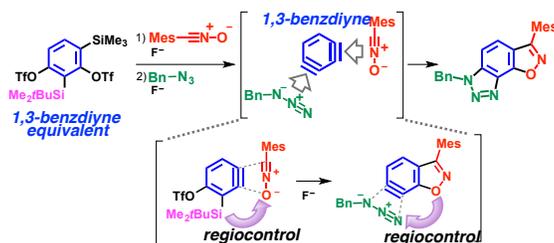
*Special Issue dedicated to Heterocyclic Chemistry

1,3- and 1,4-Benzdiyne Equivalents for Regioselective Synthesis of Polycyclic Heterocycles

Takashi Ikawa, Shigeaki Masuda, Akira Takagi and Shuji Akai

Chem. Sci. **2016**, *7*, 5206–5211.

DOI: 10.1039/c6sc00798h



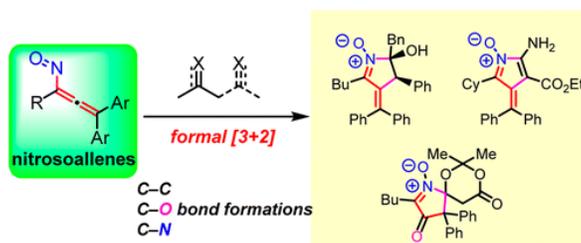
Abstract: We have devised a novel 1,3-benzdiyne equivalent, capable of quadruple functionalization by sequential benzyne generation and reaction with arynophiles. The key features of this method include the chemoselective generation of two triple bonds in a single benzene ring under fluoride-mediated mild conditions, and the regiocontrol of each benzyne reaction by the substituent next to the triple bond. This method produced various benzo-fused heteroaromatic compounds *via* reactions with arynophiles, such as furans, azides, and diazo compounds. A validation of the method is given in the convergent synthesis of the antipsychotic drug risperidone. A similar strategy has also been applied to a 1,4-benzdiyne equivalent to construct linearly benzo-fused heteroaromatics.

Formal [3+2] Cycloaddition of Nitrosoallenes with Carbonyl and Nitrile Compounds to Form Functional Cyclic Nitrones

Hiroki Tanimoto, Takashi Shitaoka, Keiichi Yokoyama, Tsumoru Morimoto, Yasuhiro Nishiyama and Kiyomi Kakiuchi

J. Org. Chem. **2016**, *81*, 8722–8735.

DOI: 10.1021/acs.joc.6b00758



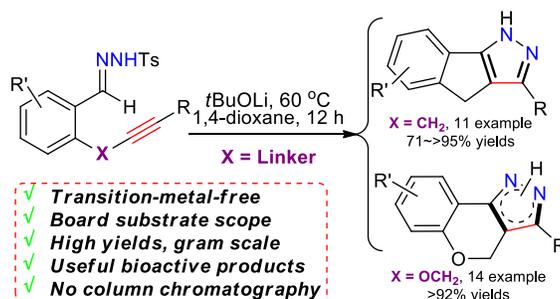
Abstract: The synthesis of functional cyclic nitrones *via* [3+2] cycloadditions of allenamide-derived nitrosoallenes with carbonyl/nitrile compounds, including ketones, esters, and nitriles, is presented herein. Rapid carbon–carbon, carbon–oxygen, and carbon–nitrogen bond formations were achieved with *in situ* prepared nitrosoallenes, and densely substituted oxacyclic and carbocyclic nitrones containing tetrasubstituted carbon centers were successfully synthesized. The spirocyclic nitronone products synthesized from cyclic dicarbonyl compounds underwent the unique skeletal rearrangements to cyclic α -ketonitrones.

1,3-Dipolar Cycloaddition of Alkyne-Tethered *N*-Tosylhydrazones: Synthesis of Fused Polycyclic Pyrazoles

Yang Zheng, Xiaolu Zhang, Ruwei Yao, Yuecheng Wen, Jingjing Huang and Xinfang Xu

J. Org. Chem. **2016**, *81*, 11072–11080.

DOI: 10.1021/acs.joc.6b02076



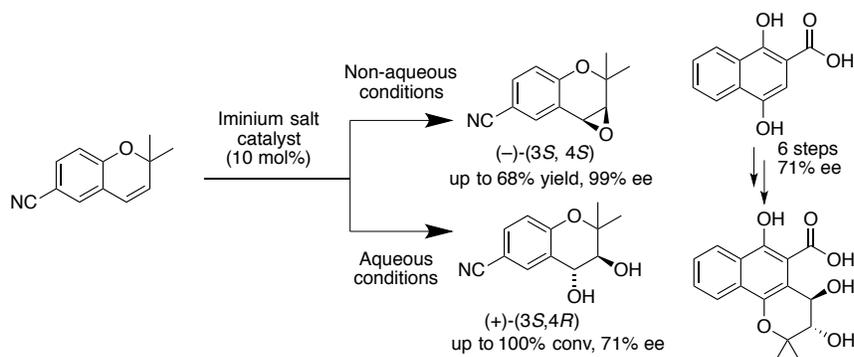
Abstract: A general and transition-metal-free access to the fused polycyclic pyrazoles via an intramolecular 1,3-dipolar cycloaddition reaction of alkyne-tethered tosylhydrazones has been reported. The pure solid products could be obtained without column chromatography in high to excellent yields, and the obtained products are useful bioactive molecules or could be used as the key intermediate for synthesis of these compounds in one or two steps. Additionally, a [3+2]-cycloaddition followed by a direct H- shift aromatization reaction mechanism was proposed, which is different from the previously reported aryl or alkyl sequential [1,5]-sigmatropic rearrangement pathway.

Asymmetric Epoxidation of Chromenes Mediated by Iminium Salts: Synthesis of Mollugin and (3*S*,4*R*)-*trans*-3,4-Dihydroxy-3,4-dihydromollugin

Philip C. Bulman Page, Yohan Chan, Abu Hassan Noor Armylisas and Mohammed Alahmdi

Tetrahedron, **2016**, *72*, 8406-8416.

DOI: 10.1016/j.tet.2016.10.070



Abstract: Organocatalytic asymmetric epoxidation of chromenes mediated by iminium salt catalysts under non-aqueous conditions provided *ees* as high as 99%. Contrastingly, reaction under aqueous conditions can form the corresponding diol products with *ees* as high as 71%. The process has been used for the synthesis of the East African medicinal plant metabolite (3*S*,4*R*)-*trans*-3,4-dihydroxy-3,4-dihydromollugin.