International Society of Heterocyclic Chemistry
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Issue 80 **August 2023**

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Issue 80 August 2023

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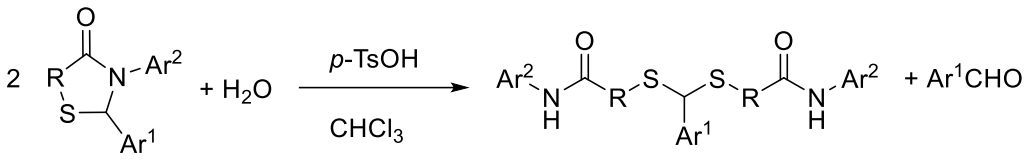
Novel conversion of 2,3-Diaryl-2,3-dihydro-1,3-thiaza-4-ones to dimeric ring-opened thioacetals

Lee J. Silverberg, Tapas Mal, Carlos N. Pacheco, Hemant P. Yennawar, Anthony Lagalante, Mark Olsen, Michael W. Russell, Elyssa N. Yeagley, Emily L. Zeigler

Results in Chemistry, **2023**, *6*, 101062. Doi: 10.1016/j.rechem.2023.101062

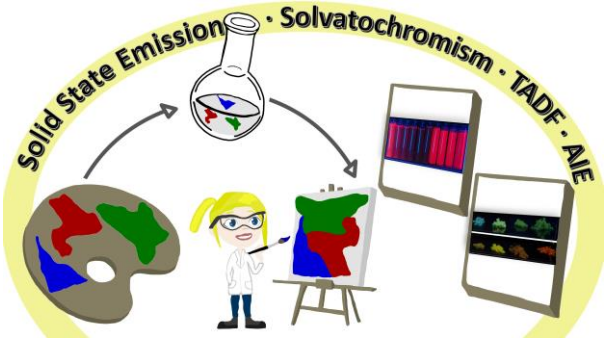


It has been found that some six and seven membered 2,3-diaryl-2,3-dihydro-1,3-thiaza-4-ones will undergo acid-catalysed reaction with water when dissolved in chloroform to give dimeric ring opened thioacetals.

Multicomponent synthesis of chromophores – The one-pot approach to functional π-systems

L. Brandner, T. J. J. Müller

Front. Chem. **2023**, *11*, 1124209. DOI: 10.3389/fchem.2023.1124209



Multicomponent reactions, conducted in a domino, sequential or consecutive fashion, have not only considerably enhanced synthetic efficiency as one-pot methodology, but they have also become an enabling tool for interdisciplinary research. The highly diversity-oriented nature of the synthetic concept allows accessing huge structural and functional space. Already some decades ago this has been recognized for life sciences, in particular, lead finding and exploration in pharma and agricultural chemistry. The quest for novel functional materials has also opened the field for diversity-oriented syntheses of functional π-systems, i.e. dyes for photonic and electronic applications based on their electronic properties. This review summarizes recent developments in MCR syntheses of functional chromophores highlighting syntheses following either the framework forming scaffold approach by establishing connectivity between chromophores or the chromogenic chromophore approach by de novo formation of chromophore of interest. Both approaches warrant rapid access to molecular functional π-systems, i.e. chromophores, fluorophores, and electrophores for various applications.

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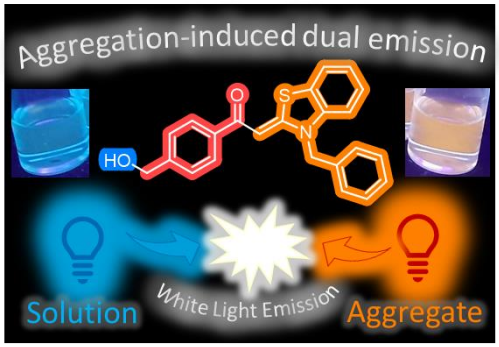
Single molecule aggregation-induced dual and white-light emissive etherified aroyl-S,N-ketene acetals via one-pot synthesis

L. Biesen, T. J. J. Müller

RSC Adv. **2023**, *13*, 16867–16871. DOI: 10.1039/d3ra02935b

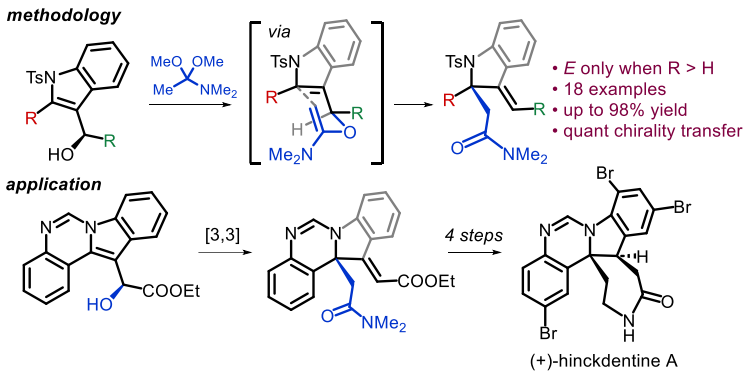


Etherified aroyl-S,N-ketene acetals are readily synthesized by a novel one-pot addition–elimination-Williamson-etherification sequence. Although the underlying chromophore remains constant, derivatives show pronounced color-tuning of solid-state emission and AIE characteristics, whereas a hydroxymethyl derivative represents an easily accessible mono molecular aggregation-induced white-light emitter.

Rapid Access to 2,2-Disubstituted Indolines via Dearomative Indolic-Claisen Rearrangement: Concise, Enantioselective Total Synthesis of (+)-Hinckdentine A

Daler Baidilov, Pavel K. Elkin, Sudhakar Athe, and Viresh H. Rawal*

J. Am. Chem. Soc. **2023**,*145*, 14831−14838. DOI: 10.1021/jacs.3c03611



The construction of 2,2-disubstituted indolines has long presented a synthetic challenge without any general solutions. Herein, we report a robust protocol for the dearomative Meerwein− Eschenmoser−Claisen rearrangement of 3-indolyl alcohols that provides efficient access to 2-substituted and 2,2-disubstituted indolines. These versatile subunits are useful for natural product synthesis and medicinal chemistry. The title [3,3] sigmatropic rearrangement proceeds in generally excellent yield and transfers the C3-indolic alcohol chirality to the C2 position with high fidelity, thus providing a reliable method for the construction of enantioenriched 2,2-disubstituted indolines. The power of this methodology is demonstrated through the concise and strategically unique total synthesis of the marine natural product hinckdentine A, which features a dearomative Claisen rearrangement, a diastereocontrolled hydrogenation of the alkene product, a one-pot amide-to-oxime conversion using Vaska's complex, and a regioselective late-stage tribromination.

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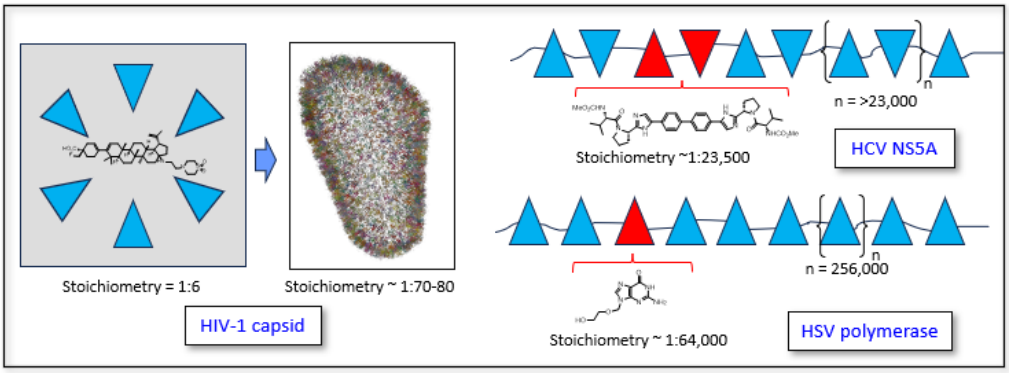
Sub-stoichiometric Modulation of Viral Targets - Potent Antiviral Agents That Exploit Target Vulnerability

Nicholas A. Meanwell*

ACS Med. Chem. Lett. **2023**, *14*, 1021-1030 DOI: 10.1021/acsmedchemlett.3c00279

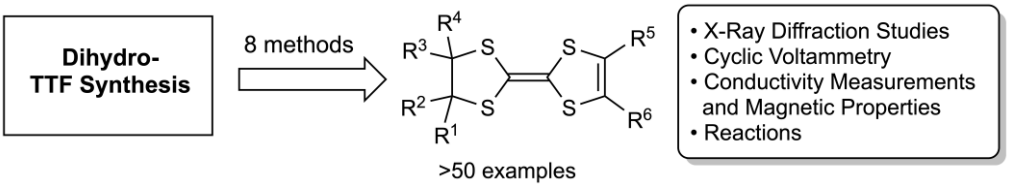


The HIV-1 maturation inhibitor fipravirimat is an example of an antiviral agent that acts at sub-stoichiometric ratio with respect to its target the viral capsid protein. Analogously, the HCV NS5A inhibitor daclatasvir has been shown to act in a highly sub-stoichiometric fashion, inhibiting viral replication at concentrations that are ~23,500 lower than that of the protein target.

Synthesis, Structure and Properties of Dihydrotetrathiafulvalenes

R. Alan Aitken* and Fiona M. Fotherby

Curr. Org. Chem. **2023**, *27*, 727–733. DOI: 10.2174/1385272827666230622155205

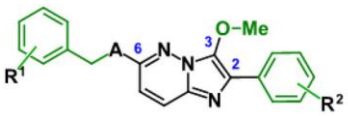


Although less well known than their fully unsaturated analogues, dihydrotetrathiafulvalenes (dihydro-TTFs) have been of considerable recent interest as components of organic conducting materials. In this article the various methods for their synthesis are reviewed and this is followed by a survey of their structure and properties, including those of charge transfer salts, and an account of their reactions.

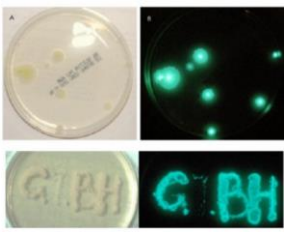
3-Methoxy-2-phenylimidazo[1,2-*b*]pyridazines highly active against *Mycobacterium tuberculosis* and *Mycobacterium marinum*

Kyle D. Farrell, Yamin Gao, Deborah A. Hughes, Robin Henches, Zhengchao Tu, Michael V. Perkins, Tianyu Zhang, Craig L. Francis

European Journal of Medicinal Chemistry **2023**, *259,* 115637. https://doi.org/10.1016/j.ejmech.2023.115637



Cmpd	Mtb MIC90 (μM)	Mm MIC90 (μM)
2b	1.26	0.15
2c	≤1.66	2.65
2d	0.63	0.63
3b	0.69	0.69
3d	0.64	0.64



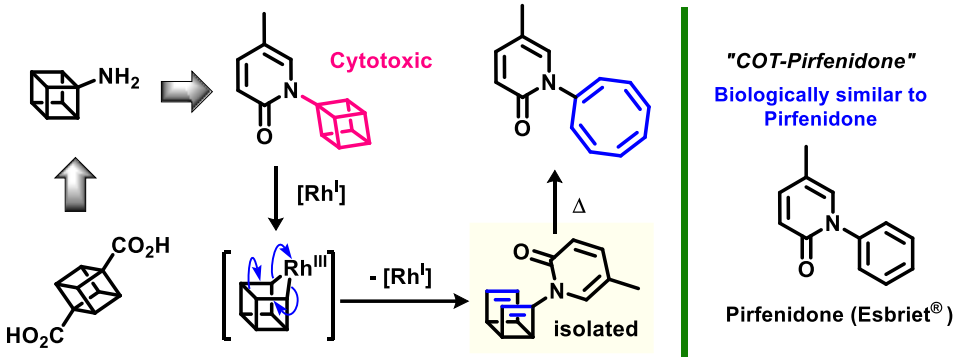
A series of 3-methoxy-2-phenylimidazo[1,2-*b*]pyridazine derivatives which were highly active against autoluminescent *Mycobacterium tuberculosis* (Mtb) and *Mycobacterium marinum* (Mm) in an *in vitro* assay were identified. SAR analysis showed that the most active compounds, which included a phenyl group bearing fluoro substituent (s) at C2, a methoxy function at C3,

and a benzyl-heteroatom moiety at C6, exhibited *in vitro* MIC_{90} values generally around 0.63–1.26 µM against Mtb and Mm. However, these compounds were inactive against Mtb *in vivo* (mice), and investigations revealed very short metabolic half-lives (<10 min) when incubated with mouse liver microsomes. Multiple observations of side products produced from oxidative cleavage of the imidazole moiety during the chemical synthesis work suggested that this is a likely metabolic pathway leading to the lack of observed activity *in vivo*.

Cubane and Cyclooctatetraene Pirfenidones – Synthesis and Biological Evaluation

Yizhou Liu, Benjamin Jian Wen Liang, Naphak Modhiran, G. Paul Savage, Daniel Watterson, Craig M. Williams*

Asian J. Org. Chem. **2023**, 12, e202300238 **DOI:** 10.1002/ajoc.202300238

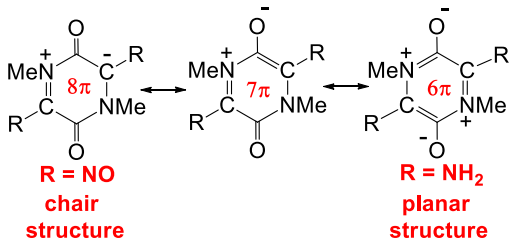


Cubane and its valence isomer, cyclooctatetraene (COT), have been widely explored as a bioisostere/motif of the phenyl ring using multiple drug templates. The development of drug repurposing during the pandemic has led to a renewed interest in pirfenidone (PFD, Esbriet®), an oral anti-fibrotic and anti-inflammatory reagent, as a treatment of post-COVID pneumonia pulmonary fibrosis. However, pirfenidone has apparent side effects and long-term administration is required. To investigate the potential changes in activity and feasibility of treating COVID-19, cubane and COT derived PFD derivatives were synthesized from aminocubane. Interestingly, the cubane derivative displayed relatively higher cytotoxicity, whereas COT-Pirfenidone showed similar performance with pirfenidone in an anti-virus and ACE2 inhibition assay, although limited potency was observed.

A DFT Study of 1,4-Diazonium-3,6-diolates: Monocyclic Representatives of Unexplored Semi-Conjugated Heterocyclic Mesomeric Betaines.

Christopher A. Ramsden* and Wojciech P. Oziminski*

Journal of Organic Chemistry, 2023, **88**, 8248-8256. https://doi.org/10.1021/acs.joc.3c00225



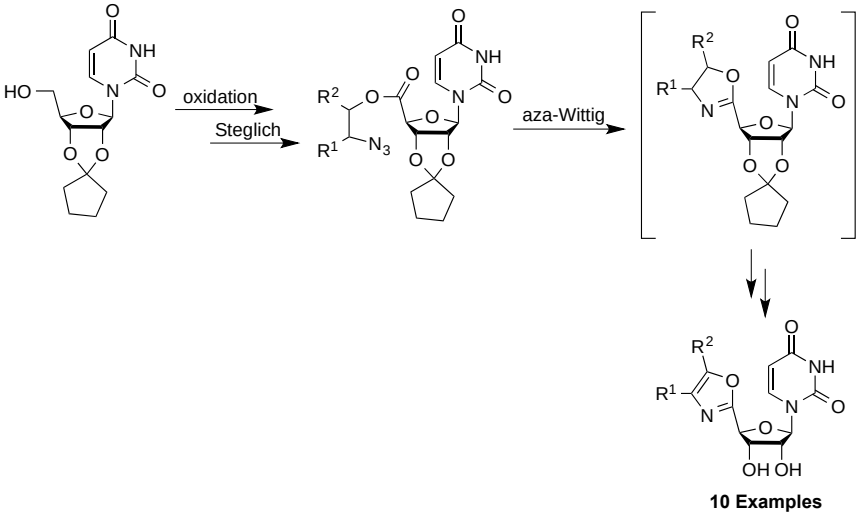
Compared to the well-known conjugated (1,3-dipolar) and cross-conjugated (1,4-dipolar) heterocyclic mesomeric betaines (HMBs), semi-conjugated HMBs are unexplored and almost unknown. The three discrete classes of HMB are defined by the connectivity between their ring 2π heteroatoms and the odd conjugated fragments that complete the ring. A single example of a stable, fully-characterised semi-conjugate HMB has been reported. This study employs DFT methodology to investigate the properties of a series of six-membered semi-conjugated HMBs. The electronic character of ring substituents is found to significantly influence the structure and electronic properties of the ring. The aromaticity, measured by HOMA and $NICS(1)_{zz}$ indices, is increased by π-electron-donating substituents whereas π-electron-withdrawing substituents decrease the calculated

aromatic character and ultimately lead to non-planar boat or chair structures. A notable property of all derivatives is the small energy gap between their frontier orbitals.

Synthesis of C4' Uridyl Aryloxazoles: A 'Heterohomologative' Approach

Paige J. Monsen, Frederick A. Luzzio*

Heterocycles **2023**, *106*, 1334-1354 DOI: 10.3987/COM-23-14873



A series of uridine-based compounds homologated at C-4' with an aryl-substituted oxazole ring were prepared. Conversion of 2',3'-O-cyclopentylidene uridine to the corresponding 4'-carboxylate followed by Steglich ester coupling with a series of azidoalcohols gave the corresponding azidoesters. The azidoesters were cyclized to the substituted oxazolines using Staudinger aza-Wittig conditions (PPh_3/THF). Direct treatment of the substituted oxazolines with nickel peroxide or DDQ provided the corresponding C4' uridyl aryloxazoles. Removal of the 2',3'- O-cyclopentylidene group was accomplished using 70% aqueous trifluoroacetic acid which afforded the target C4'-heterocyclic nucleoside analogues. The sequence could be accomplished with nitrogen or oxygen-substituted aryl azidoalcohol precursors which gave rise to the corresponding aryl-substituted C4'-oxazolyl uridine derivatives. The oxygen or nitrogen-substituted aryloxazoles underwent further derivatization to deliver ester and amide derivatives.
