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ГЕТЕРОЦИКЛЫ В ФОКУСЕ

3,6-Dihydro-2*H*-1,2-oxazines (microreview)

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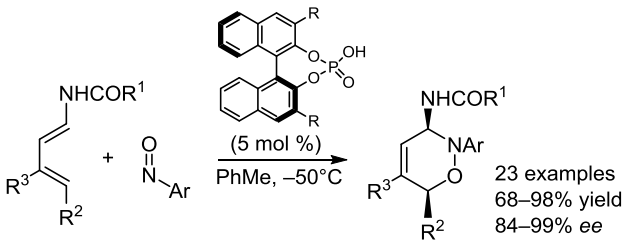
Recent synthetic methods towards 3,6-dihydro-2*H*-1,2-oxazines are reviewed. This Focus covers selected examples on the synthesis of 3,6-dihydro-2*H*-1,2-oxazines that can be grouped in the following categories: (4+2) cycloadditions, tandem reactions, formal (3+3) cycloadditions, and ring-closing metathesis.

Introduction

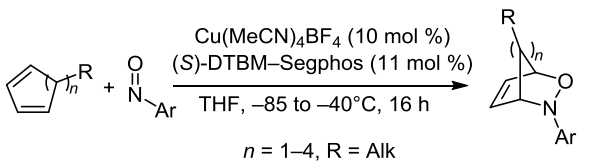
Although the first synthesis of the parent heterocycle has been reported in 1947,[1] the synthesis of functionalized analogs has attracted considerable attention in the last decade. The structure of the title compound opens several possibilities for further functionalization including (stereoselective) transformations of the C=C bond and the reductive N–O bond cleavage leading to tetrahydro-1,2-oxazines and 1,4-amino alcohols,[2] respectively. For this reason, 3,6-dihydro-2*H*-1,2-oxazines are considered as extremely useful building blocks for the preparation of more complex compounds of biological importance.[3] Here, more recent strategies towards 3,6-dihydro-2*H*-1,2-oxazines are summarized.

(4+2) Cycloaddition

The title heterocycle can be obtained by Diels–Alder chemistry starting with nitroso compounds and conjugated dienes (or their equivalents) including dendralenes,[4] borodienes,[5] sterically hindered dienes,[6] $AuCl_3$-activated allenes,[7] and solid phase-supported substrates.[8] Phosphorylated nitrosoalkenes were showed to react either as heterodiene or as dienophile.[9] In 2015, Masson described a highly regio-, diastereo-, and enantioselective approach with chiral phosphoric acids as bifunctional catalysts used in the reaction of carbamate-dienes and nitrosoarenes.[10] More recently, Cu(I)–DTBM–Segphos-catalyzed asymmetric synthesis of 1,2-oxazines from variously substituted cyclic 1,3-dienes was reported by Maji and Yamamoto.[11] For example, symmetrical dienes and pyrimidine- or pyridazine-derived nitroso compounds provided products in high yields (>90%) and excellent enantioselectivities.



Masson (2015) R^1 = OBn, OAllyl, Me; R^2 = Alk, Ar; R^3 = Alk, H



Maji & Yamamoto (2015)

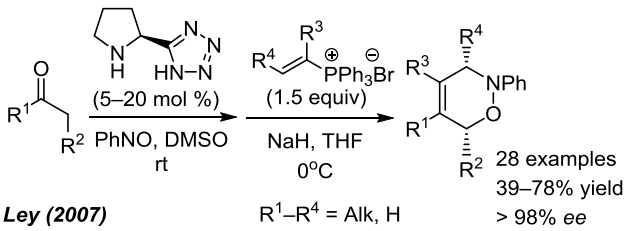
Greta Utecht was born in Łódź, Poland in 1990. She received the MSc grade in organic chemistry in 2014 working in the group of Prof. G. Mlostoń at the University of Łódź. She is a Ph.D. candidate under supervision of Dr. M. Jasiński at the Department of Organic and Applied Chemistry. Her interest focuses on carbohydrate-based approach towards polyfunctionalized 7-membered systems.

Marcin Jasiński was born in Końskie, Poland in 1980. He received his Ph.D. in chemistry in 2008 under supervision of Prof. G. Mlostoń (University of Łódź). After postdoc stays at the Freie Universität Berlin (Germany) and at the Vanderbilt University (USA) returned to Łódź. His current scientific activity covers the chemistry of thiocarbonyl compounds, lithiated alkoxyallenes, and liquid crystals.

* Здесь и далее в номере фамилия автора, с которым следует вести переписку, отмечена звездочкой.

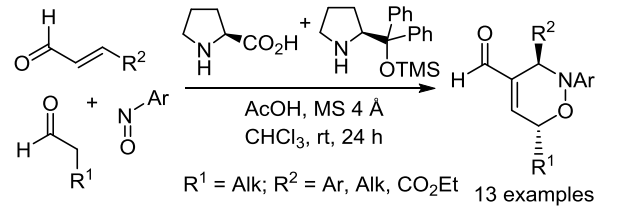
Tandem reactions

In a series of papers by Ley's group (*S*)-pyrrolidinyltetrazole was used for highly enantioselective α-aminoxylation of achiral carbonyl compounds.[12] Aminooxy carbonyl compounds generated in the first stage undergo base-promoted aza-Michael addition to phosphonium salt, followed by cyclization of the respective ylide *via* intramolecular Wittig reaction to give 1,2-oxazine.



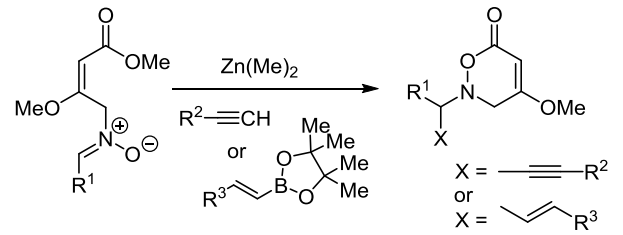
Ley (2007) R^1–R^4 = Alk, H

Similar one-pot approach to *trans*-3,6-substituted 1,2-oxazines was reported by Sun and Lin using L-proline and the Hayashi–Jørgensen's pyrrolidine as a dual organocatalytic system for highly asymmetric α-aminoxylation / aza-Michael / aldol condensation cascade reaction.[13] In this case, the intermediate analogous to that generated by Ley's method (aminooxy carbonyl compound) undergoes aza-Michael addition to α,β-unsaturated aldehyde through iminium catalysis, followed by aldol-type cyclization *via* enamine catalysis.



Sun & Lin (2012) R^1 = Alk; R^2 = Ar, Alk, CO_2Et

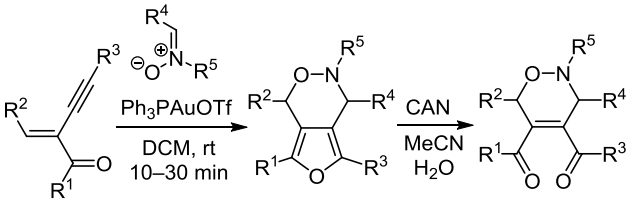
More recently, a general and efficient method for the preparation of 4,6-dioxo-1,2-oxazine ring through a tandem nucleophilic addition of organozinc reagents to a properly functionalized nitrones followed by transesterification was reported by Lei and coworkers.[14] This procedure opened up an easy access to unique heterocyclic scaffold present in natural antibiotics alchivemycin A and B.



Lei (2016) R^1 = Alk; R^2 = Alk, Ar; R^3 = Alk, Ar, H
39 examples, 45–99% yield

Formal (3+3) cycloadditions

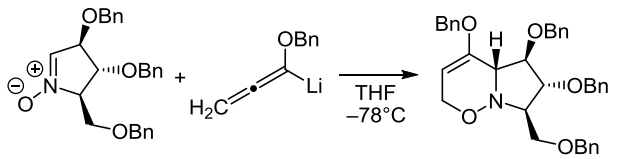
A gold(I)-catalyzed (3+3) cyclization of 2-(1-alkynyl)-2-alkenones with nitrones leading to highly substituted fused furo[3,4-*d*][1,2]oxazines has been reported in 2009.[15] The reaction proceeds *via* initially formed furanyl gold complex, which is trapped by the nitrone to afford products after subsequent cyclization. The latter could be easily converted into 4,5-diacylated 1,2-oxazines in a chemoselective manner using cerium(IV) ammonium nitrate (CAN).



R^1–R^3 = Alk, Ar; R^4–R^5 = Ar
19 examples
62–66% yield

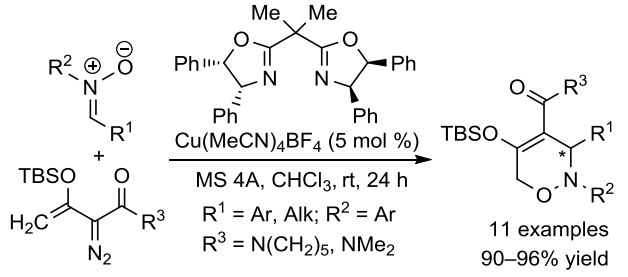
Zhang (2009) 53–95% yield, > 85:15 *dr*

Another approach to bicyclic 3,6-dihydro-2*H*-1,2-oxazines was reported by Reissig and coworkers.[16] Highly diastereoselective nucleophilic addition of lithiated alkoxyallene to enantiopure cyclic nitrones yields the corresponding allenyl hydroxylamines, which smoothly cyclize to *N*-bridged products in high yield. These compounds were used for the preparation of natural pyrrolizidine alkaloids australine and casuarine.[17]



Reissig & Goti (2013) 99% yield, > 99:1 *dr*

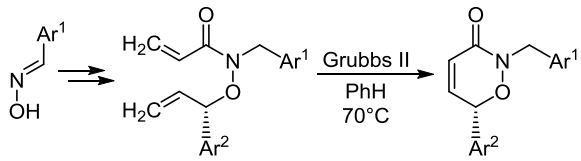
An easy access to enantiopure 3,6-dihydro-2*H*-1,2-oxazines by (3+3) annulation of aldonitrones and electrophilic vinylcarbenes derived from appropriate diazo precursors was developed by Doyle and coworkers.[18] In more recent work, enoldiazoacetamides were demonstrated as a suitable source of carbenes, which were generated in the presence of copper(I) tetrafluoroborate / bisoxazoline complex as a catalyst.[19] The reaction was performed under exceptionally mild conditions to afford title cycloadducts in excellent yield of >90% and highly enantioselective fashion.



Doyle (2016)

Ring-closing metathesis

A series of enantiopure 1,2-oxazines have been prepared by ring-closing metathesis (RCM) reactions in high yields and excellent enantioselectivity.[20] Key chiral precursors were synthesized by asymmetric Pybox/iridium-catalyzed allylic substitution followed by reduction and acylation with acryloyl chloride. Similarly to previous report,[21] the RCM proceeded smoothly with second generation Grubbs' catalyst.



Takemoto (2008)

10 examples
83–95% yield, up to 95% *ee*

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