Angewandte Highlights

Cycloadditions

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Münchnones—New Facets after 50 Years**

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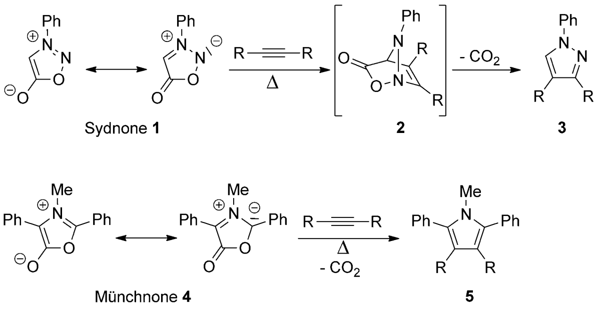
1,3-dipolar cycloadditions · alkynes · asymmetric catalysis · multicomponent reactions · pyrroles

Dedicated to Rolf Huisgen on the occasion of his birthday

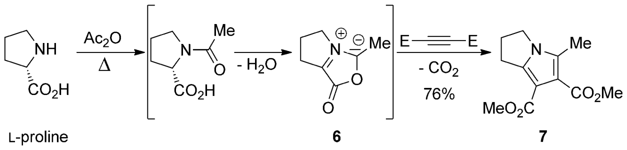
Mesoionic compounds can be represented only by mesomeric formulas with charge separation and they have been known for quite some time.[1] In the early 1960s during their search for new 1,3-dipolar compounds, Huisgen and coworkers found that alkynes undergo smooth cycloadditions with 1,2,3-oxadiazolium-5-olate **1**, an example of the class of sydnones discovered in 1935 by Earl und Mackney in Sydney,[2] and that pyrazoles **3** are formed (Scheme 1).[3]



Scheme 1. Sydnone **1** and münchnone **4** in 1,3-dipolar cycloadditions to give pyrazoles **3** and pyrroles **5**, respectively.

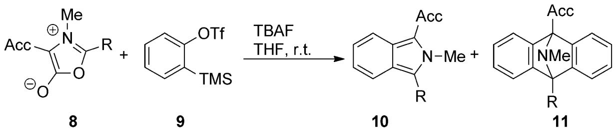
Compound **1** contains an azomethinimine moiety which in a [3+2] cycloaddition delivers bicyclic intermediate **2**; facile elimination of carbon dioxide from **2** leads to the aromatic heterocycle **3**. This discovery motivated the Munich group to prepare oxazolium-5-olate **4**, a yellow crystalline compound obtained by condensation of *N*-benzoyl-*N*-methylphenylglycine with acetic acid anhydride and which contains an azomethinylide moiety. In 1964 the Huisgen group reported that **4** and similar compounds undergo 1,3-dipolar cycloadditions with alkenes and alkynes to furnish pyrrole derivatives such as **5**.[4] The co-workers suggested the name münchnone for **4** which was later modified to describe related compounds such as imino-münchnones and phospha-münchnones. Many alkenes and hetero-dipolarophiles react with sydnones and münchnones in intra- and intermolecular 1,3-dipolar cycloadditions affording heterocyclic products.[5]

The cycloadditions of in situ generated münchnone intermediates were employed by Huisgen et al. for an efficient preparation of bicyclic compounds such as **7** (Scheme 2). The three-component reaction of L-proline, acetic acid anhydride, and dimethyl acetylenedicarboxylate provided, after *N*-acetylation and water elimination, bicyclic münchnone **6**, which was efficiently trapped by the alkyne.[6] Azlactones are formed from primary amino acids under similar conditions. They tautomerize (also under catalysis) to provide münchnones in low concentrations and hence they are also suitable precursors for 1,3-dipolar cycloadditions.



Scheme 2. Three-component reaction with münchnone **6** as an intermediate to afford the bicyclic pyrrole derivative **7**. E = CO_2Me.

After these first münchnone cycloadditions numerous applications were reported demonstrating the applicability of this elegant route to functionalized heterocycles.[5] During the last few years remarkable new aspects of münchnone chemistry were reported and a selection will be discussed here. Larock and Shi published an interesting pathway to epiminoanthracene derivatives **11** based on the reaction of acceptor-substituted münchnones **8** with aryne precursors (Scheme 3).[7] Fluoride treatment converts silylated aryl triflates **9** into arynes—again reactive intermediates with pioneering studies performed in the Munich laboratories[8]—and their cycloadditions with münchnones **8** provided mixtures of isoindoles **10** and double adducts **11**, which arise from



Scheme 3. Cycloadditions of münchnones **8** with arynes generated in situ from **9** leading to isoindoles **10** and tetracycles **11**. Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl, TBAF = tetrabutylammonium fluoride, THF = tetrahydrofuran.

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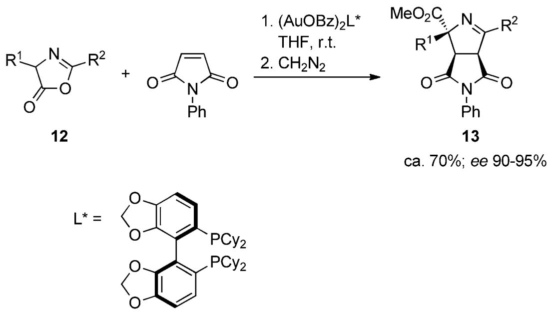
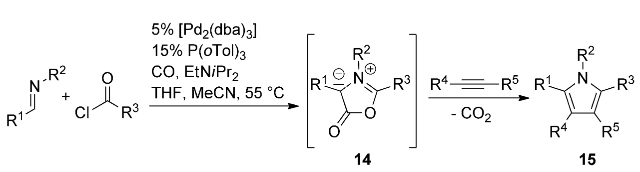
a second cycloaddition of the aryne and **10**. Depending on the stoichiometry and reaction conditions either **10** or **11** are formed in preference.

Cycloadditions of münchnones with alkenes may lead to products with stereogenic centers. Based on studies of Tepe, who converted azlactones by silver acetate catalysis into N-metalated münchnone intermediates that could be trapped by alkenes,[9] Toste et al. developed a gold-catalyzed enantioselective version (Scheme 4).[10] In the presence of alkenes, azlactones **12** were treated with 2 mol % of a gold catalyst and the Cy-SEGPHOS ligand leading to regio- and stereoselective 1,3-dipolar cycloadditions of the aura-münchnone intermediates. Spontaneous ring opening to the carboxylic acid followed by esterification with diazomethane provided highly functionalized bicyclic compounds **13** in good yields and excellent enantiomeric excesses. The resulting products are useful intermediates for further transformations.



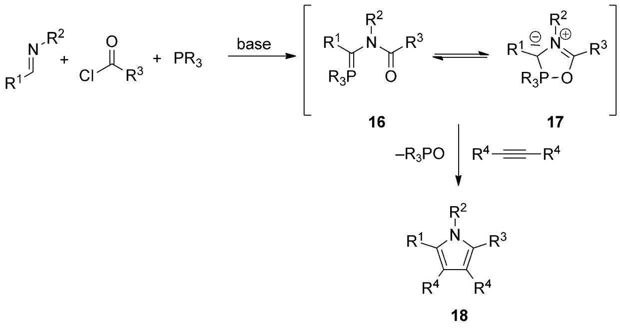
Scheme 4. Gold-catalyzed enantioselective 1,3-dipolar cycloadditions to give **13** starting from azlactones **12**. Bz = benzoyl, Cy = cyclohexyl.

A new palladium-catalyzed three-component reaction of imines, acid chlorides, and carbon monoxide generating münchnones **14** was discovered by Arndtsen and co-workers. Intermediates **14** were trapped by alkynes to form pyrroles **15** (Scheme 5).[11] This surprisingly versatile method also allows the reactions of 1,3-dipoles **14** with other π-systems.[12]



Scheme 5. Palladium-catalyzed generation of münchnones **14** and reactions with alkynes to give pyrroles **15**. dba = dibenzylideneacetone.

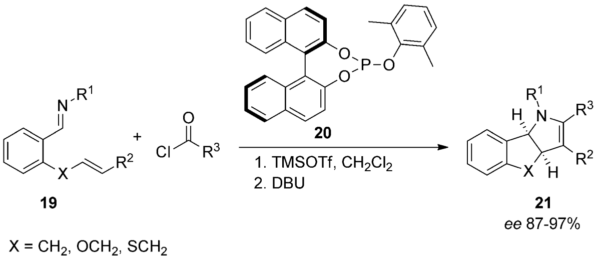
The Arndtsen group also developed methods to generate imino-münchnones[13] and phospha-münchnones.[14] Phosphorus(III) compounds and carboxylic acid chlorides combine in the presence of a base to give phosphorus ylide **16** (Scheme 6), which is in equilibrium with phospha-münchnone **17**. Since these intermediates were discovered at McGill University in Montréal, the name montréalone was proposed for them. Added dipolarophiles such as alkynes efficiently react with **17** leading to pyrroles **18** in excellent yields. Comprehensive optimization shows that catechol-substituted phosphonites are the best components for this version of phospha-münchnone generation. Instead of alkynes other dipolarophiles can be introduced as the second component. This establishes an elegant multicomponent system for the synthesis of a great variety of heterocycles. An extensive theoretical study conducted by Arndtsen, Krenske, and Houk et al. deals with the observed regioselectivity phenomena of münchnones, imino-münchnones, and phospha-münchnones.[15]



Scheme 6. Generation of phospha-münchnones (montréalones) **17** from phosphorus(III) compounds and their trapping with alkynes to give pyrroles **18**.

As latest version Arndtsen recently published an enantioselective reaction employing chiral phosphites.[16] Stoichiometric amounts of phosphite **20**, derived from (*R*)-BINOL and 2,6-dimethylphenol, formed with acid chlorides and *ortho*-alkenyl-substituted imines **19** the corresponding phospha-münchnones, that afforded in intramolecular 1,3-dipolar cycloadditions tricyclic products of type **21** (Scheme 7). The initially formed 1-pyrrolines usually undergo a proton shift to the more stable isomers **21** which were isolated in good yields and with enantiomeric excesses of up to 97 %. Currently it is unclear whether this elegant method for enantioselective synthesis of pyrrole derivatives can be extended to intermolecular reactions and whether versions will be found using the chiral promotor only in catalytic amounts. It will be exciting to find out![17]

The examples of multicomponent reactions with münchnone intermediates, the generation of phospha-münchnones (montréalones), and the enantioselective versions demon-



Scheme 7. Intramolecular enantioselective cycloadditions of phospha-münchnones (montréalones) to provide tricycles **21**. DBU = 1,5-diazabicyclo[5.4.0]undec-5-ene.

strate that much has been learned after the first use of these mesoionic compounds in cycloadditions 50 years ago. Developments in other areas of synthetic organic chemistry were picked up and used in 1,3-dipolar cycloadditions for the preparation of complex heterocycles. Will there be additional cycloadditions with other mesoionic systems in the future? And which Olympic city will be godfather of this class of compounds?

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