Mendeleev Communications

Mendeleev Commun., 2025, **35**, 512–514

Tracking the reactivity of arylideneimidazol-4-ones in the Diels–Alder cycloaddition

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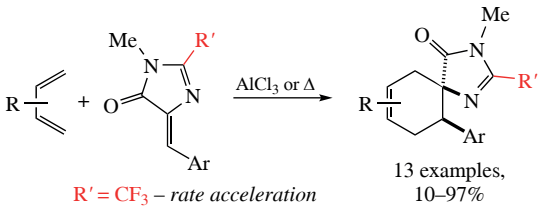
DOI: 10.71267/mencom.7781

Previously unknown [4+2]-cycloaddition of 5-arylidene-imidazol-4-ones with dienes leading to 1,3-diazaspiro[4.5]-deca-1,7-dien-4-ones is proceeding under either Lewis acid catalysis or upon thermal initiation. Arylideneimidazol-4-ones with electron-donating groups display low reactivity, which could be overcome by introduction of trifluoromethyl group in the 2-position of imidazol-4-one.



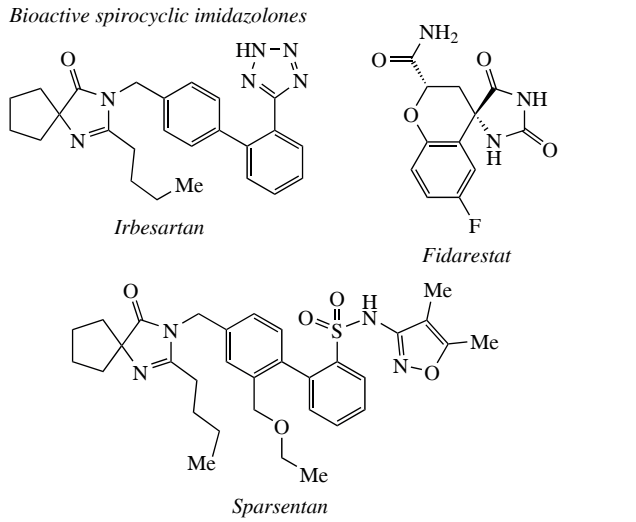
Keywords: [4+2]-cycloaddition, Diels–Alder reaction, spirocyclic compounds, catalysis, imidazol-4-one.

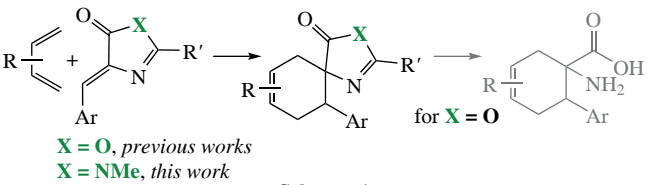
Many biologically active natural and artificial compounds have spirocyclic structure.[1] The current interest in these compounds is defined by a reduced conformational entropy penalty for them upon binding to a protein target.[2] Therefore, synthesis of spirocyclic derivatives is trending in modern medicinal chemistry.[3] Our group is focused in incorporation of imidazol-4-one and similar heterocyclic scaffolds into spirocyclic systems due to their underexplored potential in the drug design.[4,5] Such approach is inspired by the structure of already marketed drugs (Scheme 1, upper line): Irbesartan,[6] Fidarestat[7] and Sparsentan,[8] as well as recent reports on bioactive derivatives.[9–12] The most developed routes to such compounds are based on [3+2]-cycloaddition reactions, such as azomethine ylide cycloaddition,[10,13–20] nitrile oxide and nitrile imine cycloadditions,[21–26] nitrones,[27,28] formal cycloaddition of allenes[29] and some others.

Spiro systems with a six-membered cycle are rather limited. The major route toward them consists in the Diels–Alder reaction of heterocycles containing exocyclic double bond[12,30–32] or their stepwise synthetic analogs.[33,34] In previous years, the major attention was paid to oxazolone (azlactone) derivatives, labile compounds that would undergo ring-cleavage to amino acid derivatives (Scheme 1, bottom line).[35–40]

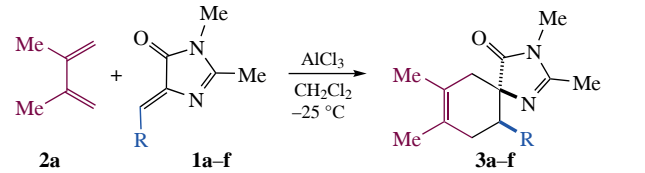
In contrast, Diels–Alder reaction of 5-alkylideneimidazol-4-ones ('eneimidazol-4-ones') is virtually unknown. These species should give stable spirocyclic derivatives, and therefore could serve useful templates for drug design. However, the presence of the second nitrogen atom in these molecules makes them more basic and also reduces their reactivity. In this work, we performed the first study of Diels–Alder reaction of eneimidazol-4-ones and established its major regularities.

A study of the Diels–Alder reaction started with an attempt to apply literature reaction conditions for azlactones[35] on model substrate **1a** (Scheme 2). We found that thermal reaction with 2,3-dimethylbutadiene **2a** was extremely slow, in contrast performing the same reaction at −25 °C under $AlCl_3$ catalysis

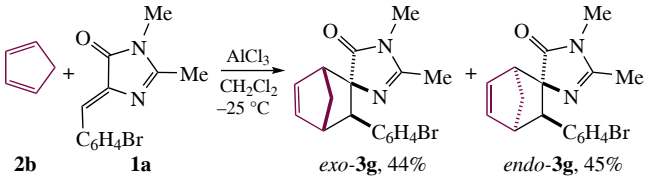




Scheme 1



a R = 4-BrC_6H_4, 55% **d** R = 4-$MeOC_6H_4$, 27%
b R = 4-$O_2NC_6H_4$, 65% **e** R = 3-ClC_6H_4, 50%
c R = Ph, 10% **f** R = 2-thienyl, 17%



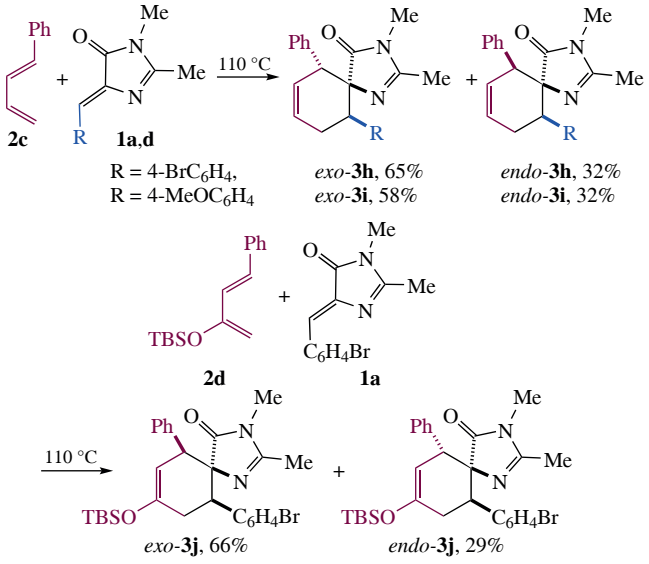
Scheme 2

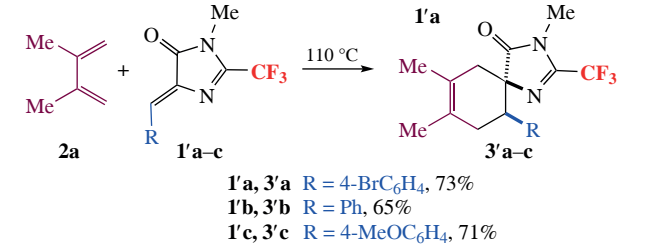
results in formation of the desired product **3a**. Screening of the catalyst (*e.g.* $TiCl_4$) and reaction conditions (solvent, temperature, for details see Online Supplementary Materials, Table S1) revealed optimal conditions.

The found reaction conditions were expanded for different arylideneimidazol-4-ones **1** (see Scheme 2). It was found that the reaction proceeded well only for derivatives **1b**,**f**, containing strong and moderate acceptor substituents. For arylideneimidazol-4-ones **1c**–**e** with donating substituents the desired products **3c**–**e** were formed in limited amounts. The use of Lewis acid as catalyst initiates polymerization of diene **2a**, so its great excess should be used. Moreover, since imidazol-4-one ring, as we have mentioned, is basic, complex of products **3** with $AlCl_3$ is hard to destroy, which leads to formation of by-products. The same reaction conditions were tested in reaction of substrate **1a** with cyclopentadiene **2b** (see Scheme 2). In this case two cycloadducts *exo*-**3g** and *endo*-**3g** are formed in 1 : 1 ratio and 97% total yield.

Such unsatisfactory results prompted us to search for realization of thermal Diels–Alder reaction. First, the reaction of more reactive dienes **2** was studied (Scheme 3, upper line). (*E*)-1-Phenylbutadiene **2c** reacts with arylideneimidazol-4-one **1a** upon reflux in toluene for 24 h with formation of two cycloadducts *exo*-**3h** and *endo*-**3h** in 2 : 1 ratio and 97% total yield. The stereochemistry of major diastereomer *exo*-**3h** was determined by single crystal X-ray diffraction analysis, which was in accordance with the least sterically hindered approach of the dienophile (Figure 1).† For the second diastereomer *endo*-**3h** the stereochemistry was assigned by assumption of the same synchronous mechanism and was further confirmed by NOESY. Nearly the same result was obtained for reaction of (*E*)-1-phenylbutadiene **2c** with electron-rich 4-methoxybenzylideneimidazol-4-one **1d** (90% yield and 1.8 : 1 *dr*), but it required longer reaction time (24 h) to achieve complete conversion. The reaction of model substrate **1a** with very reactive (*E*)-4-phenyl-2-(*tert*-butyldimethylsilyloxy)buta-1,3-diene **2d** was complete in 6 h and provided two cycloadducts *exo*-**3j** and *endo*-**3j** in 2.3 : 1 ratio and 95% total yield.

Based on this experience, we studied the thermal reaction with 2,3-dimethylbutadiene **2a**. Since original dienophiles **1** did not enter the reaction even in refluxing toluene, we proposed to enhance their reactivity by introducing acceptor group into





1′a, 3′a R = 4-BrC_6H_4, 73%
1′b, 3′b R = Ph, 65%
1′c, 3′c R = 4-$MeOC_6H_4$, 71%

Scheme 3

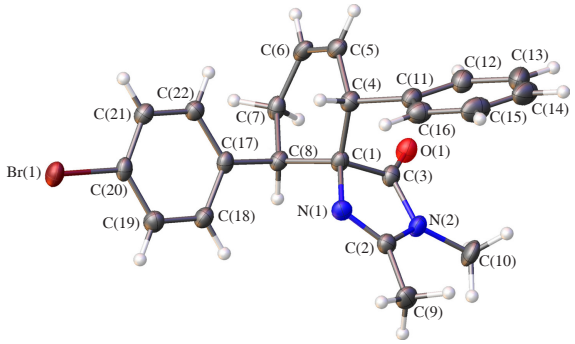


Figure 1 X-ray crystallography data for *exo*-**3h** provided at 50% probability level.

heterocyclic core (Scheme 3, bottom line). Indeed, 2-trifluoromethylimidazol-4-ones **1′a**–**c**[41] readily underwent cycloaddition with 3,4-dimethylbutadiene **2a** to give cycloadducts **3′a**–**c** in 65–71% yields. Noteworthy, even dienophiles with electron rich aromatic groups (such as **1′c**) are able to react, when trifluoromethyl group is introduced. Such acceleration effect is associated with the strong electron-withdrawing character of trifluoromethyl group, which significantly lowers energy of LUMO of dienophile and enables more stabilizing orbital interactions.

In summary, the Diels–Alder reaction of arylideneimidazol-4-ones with various dienes was studied. Although the Lewis acid catalyzed reaction is providing desired spirocyclic products, it suffers from low yields. For active dienes, the more efficient pathway consists in usual thermal activation. The substrates, which do not readily undergo thermal cycloaddition, can be preactivated *via* introduction of trifluoromethyl group at the 2-position of the imidazolone cycle.

The study was carried out with the financial support of the Russian Science Foundation (RSF grant no. 23-73-10004). A. A. Korlyukov acknowledges Ministry of Science and Higher

† *Crystal data for exo*-**3h**. $C_{22}H_{21}BrN_2O$ (M = 409.32), orthorhombic, space group *Pbca*, a = 15.7560(13), b = 13.5879(11) and c = 17.8322(15) Å, V = 3817.6(5) Å^3, μ(MoKα) = 2.166 mm^{-1}.

CCDC 2426596 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* https://www.ccdc.cam.ac.uk.

Education of the Russian Federation (contract no. 075-03-2023-642) for employing the equipment of Center for molecular composition of INEOS RAS in X-ray crystallographic study.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.7781.

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Received: 31st March 2025; Com. 25/7781