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Diene-transmissive hetero-Diels–Alder reaction of distyryl thioketone

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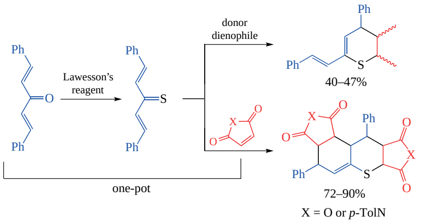
The reaction distyryl thioketone with donor alkenes (norbornene and styrene) gives adducts of the hetero-Diels–Alder reaction. In the case of maleic acid derivatives, a tandem reaction occurs which leads to polycyclic derivatives of 3,4-dihydro-2*H*-thiopyran. The stereochemical features of the ongoing transformations were examined.



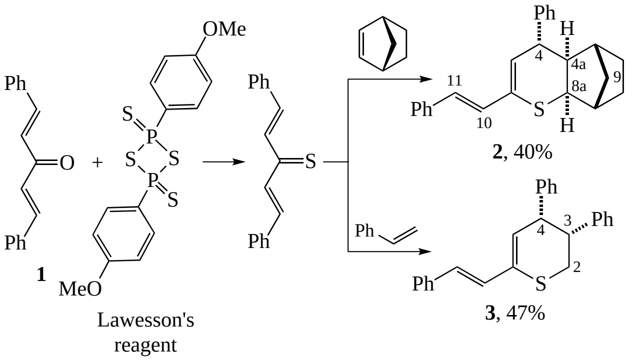
Keywords: 3,4-dihydro-2*H*-thiopyrans, hetero-Diels–Alder reaction, dienes, dienophiles, diene-transmissive reactions, Lawesson's reagent, thioketones, enethiones.

Diels–Alder reaction remains one of the most productive synthetic transformations in organic chemistry from the moment of its discovery.[1(*a*)] Numerous versions for its performance are documented[1(*b*)–(*e*)] thus providing design of complex polycyclic structures due to tandem transformations.[1(*f*)] A very interesting type of dienes represent cross-conjugated dienes or dendralenes.[1(*g*)] These dienes participating in the [2+4] cycloaddition reaction can enter into tandem Diels–Alder reaction with various dienophiles, opening an efficient pathway to molecular complexity.[1(*h*)] Such transformation is called the diene-transmissive Diels–Alder reaction. Moreover, application of unsaturated ketones, imines or thioketones permits hetero version of diene-transmissive Diels–Alder reaction. First example of diene-transmissive hetero-Diels–Alder (DTHDA) reaction has been discovered by Motoki,[2(*a*)] and later Saito proposed aza-version of DTHDA.[2(*b*)]

Cross-conjugate thioketones are highly attractive dienes for this aim due to rich chemistry of thiocarbonyls and their higher reactivity in various cycloadditions.[3(*a*)] However, examples of DTHDA with thioketones are still rare.[3(*b*)] Earlier[4–6] we developed a one-pot synthesis of 3,4-dihydro-2*H*-thiopyran derivatives with the *in situ* generation of unsaturated thioketones. In this work, we investigated the possibility of one-pot synthesis of adducts based on dibenzalacetone and stereochemical outcome of DTHDA with distyryl thioketone, sulfur analogue of dibenzalacetone.

First, the one-pot reaction between dibenzalacetone **1**, the Lawesson's reagent and electron rich dienophiles was studied (Scheme 1). The reaction with norbornene or styrene gave adducts **2**, **3** resulting from the hetero-Diels–Alder reaction even when using a double excess of the dienophile. No reaction was observed in the case of more sterically demanding dienophiles. For example, we failed to obtain cycloadducts with 5-norbornene-2,3-dicarboxylic acid derivatives (anhydride and imides)[4,6] even at 140 °C.

The reaction is completely stereoselective and regioselective in the case of styrene. The assignment of signals in the NMR spectra of compounds **2** and **3** was established by ^{1}H–^{1}H COSY, ^{1}H–^{13}C HSQC and ^{1}H–^{13}C HMBC spectroscopy methods. A long-range W-shaped interaction in the spectrum of **2** between the H(4a)–H(9) (J = 1.4 Hz) and H(8a)–H(9) (J = 1.5 Hz) protons was observed. It indicates[7] the selective formation of the *exo*-Diels–Alder adduct.[8] The value of the coupling constant $J_{\mathrm{H(4)-H(4a)}}$ = 10.8 Hz corresponds to the *trans*-arrangement of the protons. Similarly, the value $J_{\mathrm{H(10)-H(11)}}$ = 15.7 Hz corresponds to the *trans*-arrangement of the double bond. The structure of **3** was proved by the presence of 2-CH$_2$ methylene protons which have cross peaks with a carbon atom at 142.3 ppm in the ^{1}H–^{13}C HSQC spectrum. The value of $J_{\mathrm{H(3)-H(4)}}$ = 4.7 Hz indicates *cis*-arrangement of these protons. Additionally, the structure of **3** was confirmed by X-ray diffraction analysis (Figure 1). Compound **3** crystallizes in racemic non-centrosymmetric space group *Cc* (Z' = 1). In the crystal, six-membered ring is characterized by the *sofa* conformation with the deviation of C(4) atom by 0.71 Å with one phenyl in axial and other in equatorial position.[†]



Scheme 1 *Reagents and conditions*: toluene, 75 °C, 8 h.

[†] *Crystal data for* **3**. C$_{25}$H$_{22}$S (M = 354.48), monoclinic, space group *Cc* at 120 K, a = 17.8460(10), b = 11.1708(7) and c = 9.9137(5) Å, β = 105.758(3)°, V = 1902.06(19) Å^3, Z = 4, (Z' = 1), d_{calc} = 1.238 g cm^{-3}. Total of 6379 reflections were collected (4577 independent reflections, $\theta_{\max}$ = 30°, R_{int} = 0.0529). The refinement converged to R_1 = 0.0403 (for 4034 observed reflections), GOF = 1.031. The X-ray diffraction analysis was carried out on a Bruker D8 QUEST diffractometer (graphite monochromated MoK$_\alpha$ radiation, ω-scanning). Collection, editing and

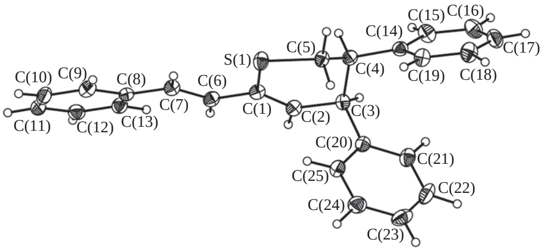
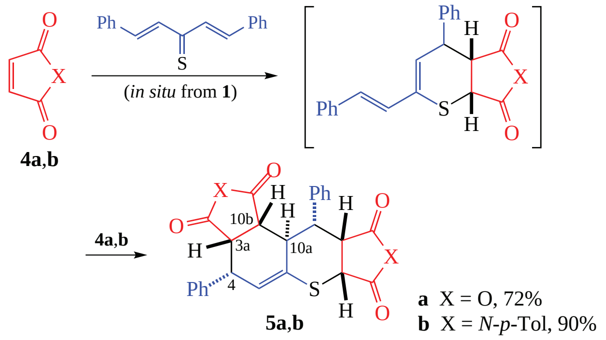


Figure 1 Molecular structure of compound **3**. Thermal ellipsoids are given at the 50% probability level.

The reaction between distyryl thioketone and maleic derivatives **4a**,**b** resulted in stereoselective formation of the double addition products **5a**,**b** (Scheme 2). The three-stage tandem reaction includes thionation followed by hetero- and carbo-Diels–Alder reactions. The stereochemical result of the *cis*-addition of the first dienophile molecule is confirmed by the value of the coupling constant between the H(9a) and H(6a) (J = 10.2 Hz for **5a** and J = 9.3 Hz for compound **5b**). The values of $J_{\mathrm{H(9a)–H(10)}}$ (3.8 Hz for compound **5a** and 3.3 Hz for compound **5b)** indicate their *cis*-arrangement,[9] whereas the $J_{\mathrm{H(10)–H(10a)}}$ values of 12.8 Hz for **5a** and 12.0 Hz for **5b** confirm the *trans*-location of these hydrogen atoms. The signals for the H(10b) and H(4) in the ^{1}H NMR spectra are overlapped multiplets. However, taking into account the literature data, an *endo*-attack can be predicted.[3(*b*)]

In accordance with electronic requirements, the tandem Diels–Alder reaction at 75 °C leads to the formation of **5** even when equimolar ratio of reagents was used. However, in the case of donor dienophiles, the reaction stops to form a carbodiene system. This opens up an interesting possibility of using two different dienophiles. Thus, the adduct of the reaction with styrene **3** enters into diene synthesis with *N*-*p*-tolylmaleimide **4b** at 140 °C (Scheme 3) to form selectively **6**. Higher activity of carbonyl-containing dienophiles in this reaction can be also explained by their activation by oxothiaphosphine oxides as a Lewis acid, which are formed from Lawesson's reagent.[6]

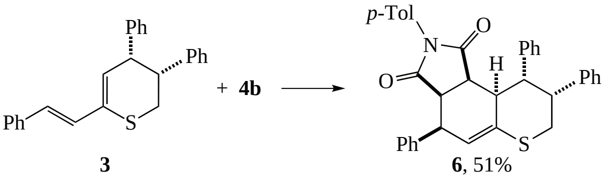


4a,**b**

5a,**b**

a X = O, 72%
b X = *N*-*p*-Tol, 90%

Scheme 2 *Reagents and conditions*: Lawesson's reagent, toluene, 75 °C, 3 h.



3

6, 51%

Scheme 3 *Reagents and conditions*: *o*-xylene, 144 °C, 12 h.

In conclusion, a simple method for the preparation of new polycyclic thiopyran derivatives was elaborated using three-stage tandem reaction of dibenzalacetone with maleic acid derivatives. The sequence includes thionation followed by hetero- and carbo-Diels–Alder reaction. The use of styrene and norbornene as dienophiles leads only to the products of the hetero-Diels–Alder reaction. All transformations proceed stereo- and regioselectively.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2022.05.031.

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refinement of unit cell parameters, as well as accounting for absorption were carried out using APEXII and SAINT PLUS programs. All calculations were carried using SHELXTL PLUS software. The structure was solved by dual methods and refined by least squares methods in the anisotropic approximation for non-hydrogen atoms.

CCDC 2123430 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.