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New 4-azatetracyclo[5.3.2.0^{2,6}.0^{8,10}]dodec-11-ene-3,5-diones *via* the cycloaddition of *N*-phenylmaleimide and cyclohepta-1,3,5-trienes

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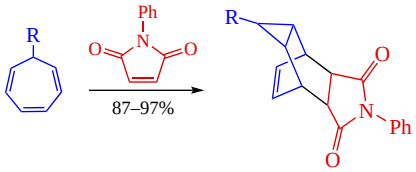
The cycloaddition reactions of *N*-phenylmaleimide with 7-substituted cyclohepta-1,3,5-trienes afforded new 4-azatetracyclo[5.3.2.0^{2,6}.0^{8,10}]dodec-11-ene-3,5-diones in high yields (87–97%). The true substrates which underwent the [4+2] cycloaddition were the 7-R-bicyclo[4.1.0]hepta-2,4-diene tautomers. The structures of the synthesized compounds were proved by NMR spectroscopy and X-ray diffraction analysis.



R = Et, Ph, CH_2=$CHCH_2$, OEt, $CH_2C(O)Me$, CN

Keywords: [4+2] cycloaddition, 7-substituted cyclohepta-1,3,5-trienes, *N*-phenylmaleimide, 4-azatetracyclo[5.3.2.0^{2,6}.0^{8,10}]dodec-11-ene-3,5-diones, diene adducts, biologically active compounds.

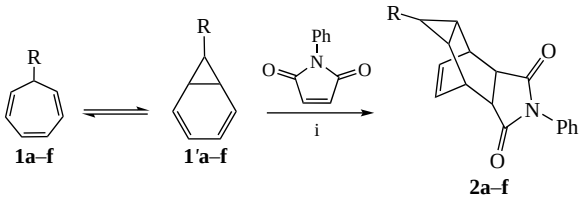
Cycloaddition reactions involving cyclohepta-1,3,5-trienes (CHTs) represent an efficient tool for the synthesis of various bridged bi- and polycyclic compounds,[1] including those used in the preparation of biologically active and medicinal compounds.[2] In these transformations, the true substrates are minor tautomeric bicyclo[4.1.0]hepta-2,4-dienes which exist in equilibrium with CHTs; only dienes having been trapped by dienophiles. The rigid bridged structure of diene adducts of CHT, containing valuable pharmacophore fragments, creates the necessary conditions for the possibility of using these molecules in the synthesis of new medicinal compounds (for the structures, see Online Supplementary Materials, Figure S1). 4-Oxatetracyclo[5.3.2.0^{2,6}.0^{8,10}]dodec-11-ene-3,5-dione obtained from maleic anhydride and CHT,[3] was used for the synthesis of an antiviral drug for the treatment of smallpox (tecovirimat, ST-246).[4] Of special interest for the development of the chemistry of medicinal compounds are diene adducts of CHTs with *N*-substituted maleimides[4,5] which contain a succinimide fragment fused to bridged polycyclic part. Therefore, the synthesis of new bridged carbocycles with a succinimide fragment based on the [4+2] cycloaddition reactions of *N*-substituted maleimides to CHTs is topical.

However, despite the obvious promise of diene synthesis based on CHTs, to date cases involving highly functionalized reactants are represented by a limited number of examples (see Online Supplementary Materials, Scheme S1).[6–11] This primarily concerns the reactions of functionally substituted CHTs with reactive dienophiles such as maleic anhydride and *N*-phenylmaleimide.[6–11] Depending on the substrate structure and reaction conditions, the yields of the adducts varied in the range of 23–90%.

Previously,[12] we investigated the [4+2] cycloaddition reactions of maleic anhydride and 7-substituted CHTs to obtain new 4-oxatetracyclo[5.3.2.0^{2,6}.0^{8,10}]dodec-11-ene-3,5-diones. Herein, we first considered the reactions of 7-substituted CHTs **1a–f** with *N*-phenylmaleimide (Scheme 1). We have established that under the developed conditions (*p*-xylene, 138 °C, 3 h), bicyclo[4.1.0]hepta-2,4-dienes **1′a–f** (valence tautomers of the CHTs) participated in the cycloaddition reaction with *N*-phenylmaleimide to give 4-azatetracyclo[5.3.2.0^{2,6}.0^{8,10}]-dodec-11-ene-3,5-diones **2a–f** in 87–97% yields.

The structures of the obtained 4-azatetracyclo[5.3.2.0^{2,6}.0^{8,10}]-dodec-11-ene-3,5-diones **2a–f** were proved by 1D (^{1}H, ^{13}C) and 2D (COSY, NOESY, HSQC, HMBC) NMR spectroscopy and X-ray crystallography. The *endo*-orientation of the imide moiety relative to the bridgehead carbon atoms C^8–C^{10} was proved by the presence of cross-correlations between the C(8)H, C(10)H and C(2)H, C(6)H proton signals in the ^{1}H–^{1}H NOESY experiment (Figure 1). The *syn*-orientation of the cyclopropane ring relative to the double bond was confirmed by the presence of cross-peaks between the signals of the C(9)H proton and the C(11)H and C(12)H protons at the double bond in the ^{1}H–^{1}H NOESY spectrum (see Figure 1).

Structures of compounds **2a**,**e** with 9-positioned ethyl and acetonyl substituents, respectively, were ultimately establishedy by X-ray diffraction (Figure 2).† Compounds **2a** and **2e** crystallize in the monoclinic system with one molecule in the asymmetric



a R = Et, 95%
b R = Ph, 97%
c R = CH_2=$CHCH_2$, 93%
d R = OEt, 89%
e R = $CH_2C(O)Me$, 92%
f R = CN, 87%

Scheme 1 *Reagents and conditions*: i, *p*-xylene, reflux, 3 h.

† *Crystal data for* **2a**. $C_{19}H_{19}NO_2$ (*M* = 293.35), monoclinic, space group $P2_1/c$, a = 19.9614(11), b = 6.3031(4) and c = 12.6364(8) Å, α = 90°, β = 102.019(5)°, γ = 90°, V = 1555.04(17) Å^3, Z = 4, d_{calc} = 1.253 g cm^{-3}, μ(MoKα) = 0.081 mm^{-1}, F(000) = 624.0. Total of 38495 were collected

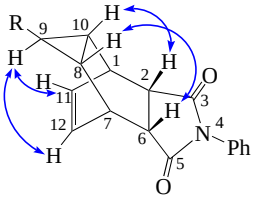


Figure 1 Key NOESY (↔) correlations for compounds **2a**–**f**.

unit. The stereogenic centers at C(1), C(2), C(6), C(7), C(8) and C(10) in both molecules have the *S**, *S**, *R**, *R**, *R** and *S** configurations, respectively. The C(3)–N(4), C(5)–N(4), C(3)=O(1), and C(5)=O(2) bonds of the imide moiety in **2a** and **2e** have similar lengths and, in the case of **2a**, they are 1.3945(15), 1.3960(15), 1.2080(15), and 1.2049(15) Å, respectively. The five-membered ring containing the imide group has a planar structure, the root-mean-square deviation of atoms from the plane of the ring in structures **2a** and **2e** differs slightly and is 0.021 and 0.026 Å, respectively. It should be noted that in the ring system of bicyclo[2.2.2]octene, both C(9) and atoms of the imide group occupy the *exo* position relative to the atoms of the C(11)=C(12) alkene bridge. The five-membered and phenyl rings do not lie in the same plane, the torsion angle C(5)–N(4)–C(1)′–C(2)′ is 57.18(19) and 49.42(15)° for **2a** and **2e**, respectively.

In conclusion, the diene synthesis reactions between *N*-phenylmaleimide and 7-substituted CHTs afforded new

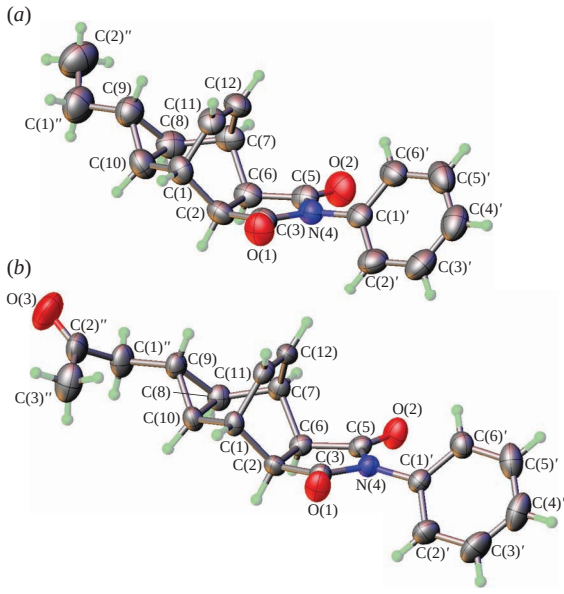


Figure 2 Molecular structure of compounds (*a*) **2a** and (*b*) **2e**. Displacement ellipsoids are drawn at a 50% probability level.

(7962 independent reflections, R_{int} = 0.0526) and used in the refinement, which converged to wR_2 = 0.2144, GOOF 1.020 for all independent reflections [R_1 = 0.0802 was calculated for 3526 reflections with $I > 2\sigma(I)$].

Crystal data for **2e**. $C_{20}H_{19}NO_3$ (M = 321.36), monoclinic, space group $P2_1/n$, a = 14.7312(6), b = 6.4502(2) and c = 17.9286(8) Å, α = 90°, β = 109.229(5)°, γ = 90°, V = 1608.52(12) Å^3, Z = 4, d_{calc} = 1.327 g cm^{-3}, μ(MoKα) = 0.089 mm^{-1}, F(000) = 680.0. Total of 39823 were collected (8177 independent reflections, R_{int} = 0.0507) and used in the refinement, which converged to wR_2 = 0.1828, GOOF 1.029 for all independent reflections [R_1 = 0.0629 was calculated for 4050 reflections with $I > 2\sigma(I)$].

CCDC 2343534 (**2a**) and 2343300 (**2e**) contain 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.

4-azatetracyclo[5.3.2.0^{2,6}.0^{8,10}]dodec-11-ene-3,5-dione derivatives with high yields (87–97%). The synthesized diene adducts are of interest as promising intermediates in the total synthesis of new biologically active and medicinal compounds.

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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.2024.09.024.

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