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Different addition modes of cyclopentadiene and furan at methylidene(thio)hydantoins

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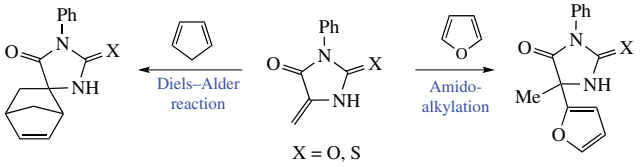
3-Methylidene-5-phenylhydantoin and 3-methylidene-5-phenylthiohydantoin react with cyclopentadiene forming spirocyclic Diels–Alder adducts. In contrast, their reactions with furan in the presence of $AlCl_3$ give the products of the furan α-amidoalkylation.



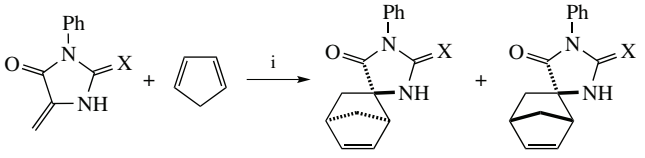
Keywords: hydantoins, thiohydantoins, Diels–Alder reaction, α-amidoalkylation, X-ray.

Hydantoin and thiohydantoin derivatives are known as biologically active substances with antidepressant,[1] anticonvulsant,[2] anti-inflammatory,[3] anti-fibrolytic,[4] anticancer,[5] antibacterial[6] and antimalarials[7] activities. A promising way for their modification is introduction of additional spiro fused fragments that would limit the conformational mobility of the molecule and can lead to a significant increase in biological activity.[8–12] The products of the Diels–Alder reactions of methylideneimidazolones with cyclic dienes potentially allow one to obtain spiro fused structures with a conformationally rigid bicyclic framework containing a reactive C=C double bond, which opens the way for further modification of target compounds. Taking this into consideration, we herein investigated the possibility of synthesizing (thio)hydantoin and spiro derivatives containing cage fragments by the reactions of 5-methylidene(thio)hydantoins with carbo- and heterocyclic dienes such as cyclopentadiene and furan.

Starting methylideneimidazolones **1** and **2** were obtained as described.[13,14] Their reactions with cyclopentadiene were performed by refluxing in methanol for ~6 h with the complete conversion of the starting imidazolones. As a result, the Diels–Alder adducts **3** and **4** were obtained in good yields (Scheme 1).

The reaction conditions (the reactant ratio, solvent and temperature) were optimized with hydantoin **1** as the model substrate. It turned out to be optimal to use an 8-fold excess of the diene in boiling chloroform, benzene, methanol or ethanol; in DMSO, acetonitrile, acetone or ethyl acetate, the reaction proceeded slowly or almost did not take place.

Reactions with cyclopentadiene for each of dienophile **1**, **2** afforded two diastereomeric products **3a**, **4a** and **3b**, **4b**,



1 X = O
2 X = S

3a X = O, 81%
4a X = S, 79%

3b X = O, 9%
4b X = S, 8%

Scheme 1 *Reagents and conditions*: i, MeOH, reflux, 6 h.

respectively, which could be separated by column chromatography. As for other methylideneimidazolone derivatives,[15] adducts **3a**, **4a** with the amide nitrogen of imidazolone in the *endo* position of the norbornene ring are predominantly formed. ^{1}H NMR spectra of compounds **3a**, **4a** contain characteristic double doublets for HC=CH protons in the range of 6.2–6.6 ppm while similar protons of minor isomers **3b**, **4b** resonate in the range of 6.1–6.4 ppm.

The structure of the main reaction product with cyclopentadiene **3a** was proven by X-ray diffraction analysis.† Dihedral angle between the planes of the cycles at spiro junction are close to 80° while hydantoin five-membered cycle is nearly planar (Figure 1).

In contrast to cyclopentadiene, furan did not undergo the [4+2]-cycloaddition reactions with compounds **1** and **2**, apparently due to the relative stability of the furan heteroaromatic system. We tested several Lewis acids such as $BF_3 \cdot Et_2O$, $AlCl_3$ and $CuCl_2$ as possible catalysts for this Diels–Alder reaction. When using $CuCl_2$, the reaction did not proceed even with a 100-fold excess of furan while in the presence of $BF_3 \cdot Et_2O$ furan was rapidly decomposed. The use of $AlCl_3$ with the simultaneous mixing of all the reactants also caused gradual

† *Crystal data for* **3a**. $C_{15}H_{14}N_2O_2$ (M = 254.28), triclinic, space group $P\bar{1}$ at 293(2) K, a = 6.2292(3), b = 9.5107(5) and c = 22.7896(8) Å, α = 78.582(3)°, β = 82.750(4)°, γ = 76.124(4)°, V = 1280.40(11) Å^3, Z = 4, d_{calc} = 1.319 g cm^{-3}, μ(MoKα) = 0.722 mm^{-1}, F(000) = 536. Total of 14894 reflections were collected and 4837 independent reflections with $I > 2\sigma(I)$, R_{int} = 0.0720 were used in the refinement, which converged to wR_2 = 0.1239, GOOF 1.086 for all independent reflections [R_1 = 0.0500 was calculated for 3218 reflections with $I > 2\sigma(I)$]. The measurements were performed on a STOE diffractometer with Pilatus100 K detector and CuKα radiation (λ = 1.54186 Å). The structure was solved by direct methods, and the non-hydrogen atoms were located from the trial structure and then refined anisotropically with SHELXTL using full-matrix least-squares procedures based on F^2 values. Hydrogen atom positions were fixed geometrically at calculated distances and allowed to ride on the parent atoms.

CCDC 2040280 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.

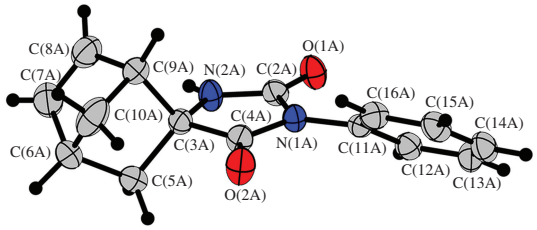
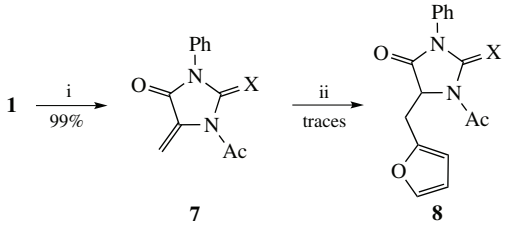


Figure 1 Molecular structure of compound **3a** (thermal ellipsoids are given with 40% probability).



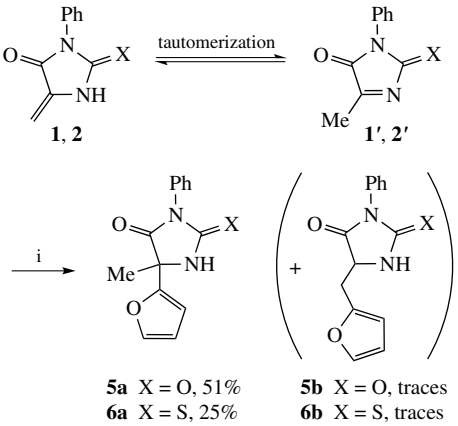
Scheme 3 *Reagents and conditions*: i, Ac_2O, NEt_3, DMAP, CH_2Cl_2, room temperature, 24 h; ii, furan, $AlCl_3$, CH_2Cl_2, room temperature, 24 h.

decomposition, however short keeping of the furan-$AlCl_3$ mixture followed by the addition of methylideneimidazolones gave adducts **5a**, **6a** in moderate yields (Scheme 2). Apparently, in this way furan in the reaction with compounds **1**, **2** underwent α-amidoalkylation instead of expected cycloaddition. It can be assumed that the reaction proceeds according to the mechanism described for the reactions of α-amidoacrylates with five-membered heterocycles.[16] Under the action of Lewis acid, the enamine–imine equilibrium of methylideneimidazolones shifts towards the imine forms **1′**, **2′** (see Scheme 2), which effectively interact with activated furan–$AlCl_3$ complex to form the α-amidoalkylation products **5a**, **6a**. In the NMR spectra of the reaction mixtures, the trace amounts of the Michael addition products **5b**, **6b** formed from the predominant enamine tautomer were also detected. The comparatively lower yields of products **6** obtained from methylidenethiohydantoin **2** relatively to its oxygen analogue **1** may be associated with the weaker acceptor properties of the double C=S bond and the possible partial hydrolysis of the thioamide fragment in the course of the final aqueous work up.

In the ^{1}H NMR spectra of products **5a** and **6a**, the characteristic singlets for the methyl group at ~1.9 ppm, as well as two doublets and a double doublets for α-substituted furans were observed. Michael adducts **5b** and **6b** are characterized by the ABX spin system in the region of 3.0–4.5 ppm.

To confirm the proposed mechanism of amidoalkylation, we synthesized an acylated methylidenehydantoin derivative **7** incapable of imine–enamine tautomerism (Scheme 3). Indeed, compound **7** did not essentially react with furan in the presence of $AlCl_3$; only the inseparable traces of the Michael adduct **8** were detected in the NMR spectrum of the crude material while only the starting imidazolone **1** and furan polymerization products could be ultimately isolated.

In summary, the reactions of 5-methylidene-2-chalcogeno-imidazolidin-4-ones with cyclic dienes, *viz*. cyclopentadiene and furan, proceed in different ways. With cyclopentadiene, tricyclic cage structures with a spiro junction of cycles are formed



Scheme 2 *Reagents and conditions*: i, furan, $AlCl_3$, CH_2Cl_2, room temperature, 24 h.

whereas the reaction with furan in the presence of a Lewis acid ($AlCl_3$) proceeds predominantly as α-amidoalkylation of furan.

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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.2021.03.034.

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