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Stereoselective synthesis of 3a,7a-dihydro-3*H*,4*H*-furo[3,4-*c*]pyran-1-ones via intramolecular hetero-Diels–Alder reaction ☆

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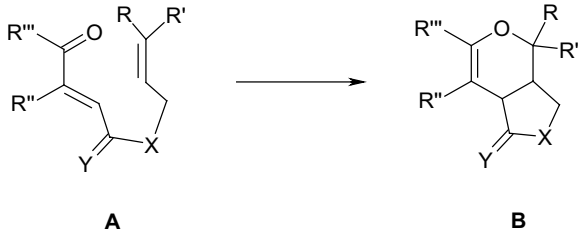
Abstract—The synthesis of 3a,7a-dihydro-3*H*,4*H*-furo[3,4-*c*]pyran-1-ones via an intramolecular hetero-Diels–Alder reaction of easily accessible α,β-unsaturated γ-ketoesters was investigated. The reaction was found to proceed in a highly stereoselective way leading to single, *cis*-configured product isomers. The same diastereomer is formed, independently of the configuration of the enone double bond of the precursor. The respective *E*- and *Z*-isomers react either through an *endo-E-syn* or an *exo-Z-syn* transition state.

The hetero-Diels–Alder reaction is one of the most important reactions for the construction of heterocyclic six-membered rings.[1–4] Its concerted character allows the selective formation of up to three stereogenic centers in a single reaction step. The intramolecular version of the hetero-Diels–Alder reaction (e.g., of α,β-unsaturated ketones, such as **A** in Scheme 1) leads to the formation of bicyclic dihydropyrane derivatives (**B**). During the course of our work aimed at the construction of polycyclic natural product-like scaffolds, we became interested in the synthesis of furo[3,4-*c*]pyranones. Dihydro- and perhydropyranes are common substructures of many natural products. Among others, they constitute an essential part of the *iridoids*, a wide-spread class of natural compounds.[5–7] Starting from an ester (cf. Scheme 1, X, Y = O), furo[3,4-*c*]pyranones should become accessible through an intramolecular hetero-Diels–Alder reaction. This type of cyclization has been observed as a side reaction during the investigation of intramolecular *ene*-reactions of α,β-unsaturated esters of allylic alcohols by *Snider* et al.[8] The intramolecular hetero-Diels–Alder reaction has been used in the synthesis of the monoterpen glycoside *secologanin*, a key intermediate in the biosynthesis of many iridoid-derived alkaloids.[5,9] More recently, Murray and coworkers have reported on the synthesis of pyranopyrrolidinones using an intramolecular hetero-Diels–Alder reaction.[10,11] Furthermore, Aungst and Funk used an intramolecular hetero-Diels–Alder reaction in the total synthesis of (±)-euplotin A.[12] To our knowledge, however, no general method leading to furo[3,4-*c*]pyranone derivatives has been reported thus far. We therefore investigated this potential route with regard to the chemistry as well as the stereochemical course of the reaction.



Scheme 1. Intramolecular hetero-Diels–Alder reaction.

The synthesis of the required building blocks was straightforward. The diethyl phosphonate esters **1a**–**c** were prepared through an *Arbuzov* reaction of the corresponding α-bromoacetates[13–15] with triethyl phosphite.[15,16] The phosphonates were converted into the α,β-unsaturated γ-ketoesters **2a**–**g** via the Horner–Wadsworth–Emmons reaction using commercially available α-diketones (see Table 1). Products **2a**–**g** were obtained as isomeric mixtures (*E*:*Z*-ratio approximately 1:2). In the cases where separation of the *E*- and *Z*-isomers (i.e., for **2a**, **b** and **e**) was possible, the pure

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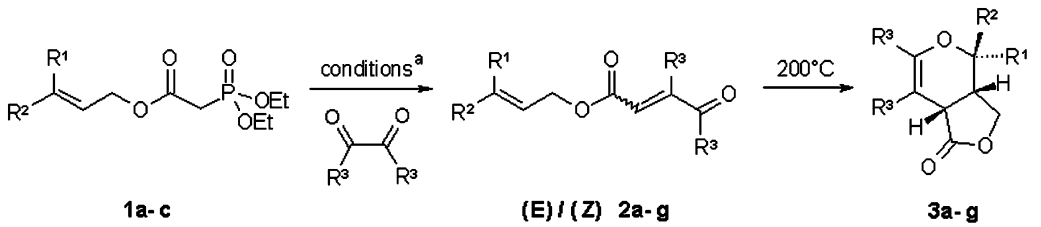
Table 1. Preparation of furo[3,4-*c*]pyranones (±)-**3a**–**g** via intramolecular hetero-Diels–Alder reaction of α,β-unsaturated γ-ketoesters **2**



R^1	R^2	R^3	Compound [yield (%); *E*:*Z*][b]	Product	Yield[c] (%)
H	H	CH_3	**2a** (62; 1:2)	**3a**	(traces)
CH_3	CH_3	CH_3	**2b** (73; 1:2)	**3b**	37 from *E*-**2b** 46 from *Z*-**2b**
CH_3	CH_3	Phenyl	**2c** (58; 1:2.3)	**3c**	58
CH_3	CH_3	4-Fluorophenyl	**2d** (42; 1:2.6)	**3d**	64
H	Phenyl	CH_3	**2e** (67; 1:2)	**3e**	21 from *E*-**2e** 69 from *Z*-**2e**
H	Phenyl	Phenyl	**2f** (38; 1:2.4)	**3f**	72
H	Phenyl	4-Fluorophenyl	**2g** (43; 1:2)	**3g**	56

[a] LiHMDS (1.1 equiv), THF, −78 °C, 2.5 h.
[b] *E*- and *Z*-isomers could be separated in the case of **2a**,**b** and **e**; all other compounds **2** were isolated as *E*/*Z*-mixtures.
[c] Isolated yields of **3** starting either from the pure *E*- or *Z*-isomers of **2b** and **e** or, alternatively, from the *E*/*Z*-mixture.

isomers were used in the following cyclization step. In all other cases, the obtained mixture of *E*- and *Z*-isomers was used.

We then investigated the thermal cyclization of α,β-unsaturated γ-ketoesters **2a**–**g**. Generally, the reaction was carried out in an autoclave at a temperature of 200 °C using toluene as the solvent. As can be seen from Table 1, the yield of the reaction increased with the number of substituents of the ene-moiety (R^1 and R^2). Only traces of product (<10%) were observed in the case of the allylesters *E*- and *Z*–**2a**. With the dimethyl and phenyl substituted derivatives, the reaction proceeded considerably better and, with one exception (*E*–**2e**), the expected products could be isolated in yields between 40% and 70%. The finding that alkyl or aryl substituents at the ene-part have a positive effect on this *inverse electron demand* hetero-Diels–Alder reaction is well in agreement with the theory.[4] Some decomposition (ester cleavage) of the starting material at the relatively high reaction temperature was observed, which partly explains the moderate yields in some cases. Attempts to facilitate the reaction with various *Lewis* acids (e.g., Cu(II), Zn(II), Al(III), BF_3) were not successful and led to complex reaction mixtures at temperatures above 110 °C. Furthermore, we could not observe any product arising from an ene-reaction,[17] which is theoretically possible with compounds **2b**, **c** and **d**. An intramolecular ene-reaction was observed by Snider et al. in a related system.[8]

As expected, the cyclization reaction turned out to be highly stereoselective. In all cases, formation of a single product was observed. Structural elucidation revealed a *cis*-configuration of the two rings. Furthermore, in the cases in which R^1 and R^2 were different (i.e., products **2e**–**g**) again a single diastereomer was formed. Most importantly, the formation of the product did not depend on the geometry of the diene moiety. The same isomer was formed from either the *E*- or the *Z*-precursor. The relative configurations of the products **3c** and **3f** were established by X-ray crystallography. The structure of **3f** is shown in Figure 1.

Based on the structural information, the stereochemical course of the hetero-Diels–Alder reaction must proceed as illustrated in Scheme 2. Since both geometrical isomers afford the same product, the *E*-isomer reacts via the *endo-syn* and the *Z*-isomer via the *exo-syn* transition state.[18,19] The formation of *trans*-fused products would require reaction through the *exo-E-anti* transition state. This has been observed in an intramolecular hetero-Diels–Alder reaction of a more flexible system leading to two annulated six-membered rings.[18] In the present case, however, the sterically less flexible five-membered linker seems to disfavor this transition state. The final fourth theoretical possibility (i.e., the *endo-Z-anti* transition state) is not possible for geometrical reasons (cf. Tietze et al.[18]).

In conclusion, *cis*-fused furo[3,4-*c*]pyranones have been synthesized from easily accessible α,β-unsaturated γ-ketoesters via an intramolecular hetero-Diels-Alder reaction. The reaction proceeds in a highly stereoselective way. Independently of the enone double bond configuration, a single product diastereomer is formed.

General procedure for preparation of α,β-unsaturated γ-ketoesters **2a**–**g**: To a stirred solution of *n*-butyllithium (1.1 equiv) in absolute THF at 0 °C under a nitrogen atmosphere, HMDS (1.2 equiv) was added. After 30 min, a solution of the corresponding diethylphosphorylacetic acid ester (**1a**–**c**, 1 equiv) in THF was added dropwise. The mixture was cooled to −78 °C and a solution of the corresponding α-dione (1.1 equiv) in

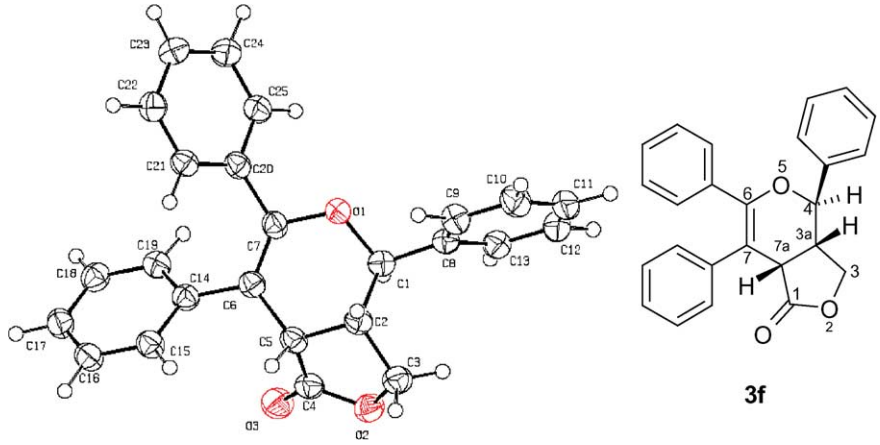
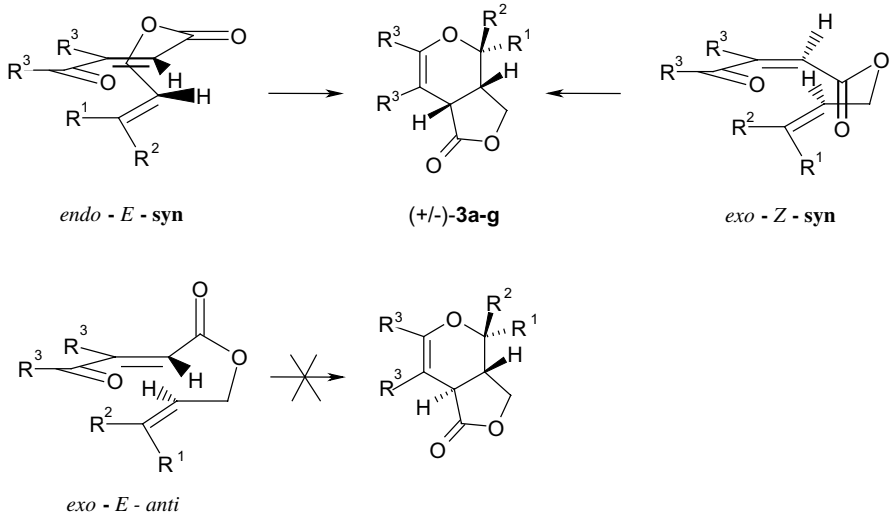


Figure 1. Relative configuration of hetero-Diels–Alder product (±)-**3f** as determined by X-ray crystallography. (Note that the crystallographic numbering, which has been kept for reasons of simplicity, is different from the systematic numbering.)



Scheme 2. Stereochemical course of intramolecular hetero-Diels–Alder reaction leading to *cis*-fused furo[3,4-*c*]pyranones.

THF was added. After stirring for 2.5 h, the solution was quenched with sat. aq. NH_4Cl. The mixture was extracted twice with CH_2Cl_2. The combined organic phases were dried (Na_2SO_4) and concentrated. The obtained crude material was purified by column chromatography (silica gel, EtOAc–hexane).

General procedure for intramolecular hetero-Diels–Alder reactions (*furo[3,4-c]pyranones* **3a**–**g**): A solution of α,β-unsaturated γ-ketoesters **2a**–**g** in toluene (10 mL per 100 mg of **2**) was placed in a Teflon® reaction chamber inside a sealed steel autoclave. After heating at 200 °C for 1–3 days the solvent was removed in vacuo and the product was purified by column chromatography (EtOAc–hexane).

Crystallographic data (excluding structure factors) for the structures **3c** and **3f** have been deposited with the Cambridge Crystallographic Data Centre as Supplementary publications numbers CCDC 233713 and CCDC 233714, respectively.

Acknowledgements

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