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Knoevenagel condensation of cyclic ketones with benzoylacetonitrile and *N*,*N*′-dimethylbarbituric acid. Application of sterically hindered condensation products in the synthesis of spiro and dispiropyrans by hetero-Diels–Alder reactions

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ABSTRACT

Inverse-electron demand Diels–Alder cycloadditions of sterically hindered cycloalkylidene derivatives of benzoylacetonitrile and *N*,*N*′-dimethylbarbituric acid with enol ethers, cyclic enol ethers and also sterically hindered cycloalkylidenecycloalkanes were investigated. New spiro, dispirodihydropyrans, spirouracils, and dispirouracils were obtained. To confirm the experimental results, frontier orbital HOMO and LUMO energies of heterodienes and dienophiles were calculated by semi-empirical AM1, PM3 methods and ab initio Hartree–Fock calculations.

1. Introduction

Cycloaddition reactions provide rapid and elegant methods for the construction of mono- and polycyclic systems. The development of new cycloreactants is a continuous challenge in the field of pericyclic reactions. The use of hetero-substituted diene and dienophiles is of specific interest for the application of Diels–Alder cycloadditions toward natural and biologically active product synthesis.[1] Reports in this area mainly concern the use of heterodienes with different substituents, but none have reported the use of sterically hindered cycloalkylidene derivatives of heterodienes. Pyran derivatives are common structural subunits in a variety of important natural products, including carbohydrates, alkaloids, polyether antibiotics, pheromones, and iridoids.[1] Also fused uracils, such as pyrano[2,3-*d*]pyrimidines, pyrido[2,3-*d*]pyrimidines, pyrazo[3,4-*d*]pyrimidines or pyrimido[4,5-*d*]pyrimidines are reported to have a wide range of biological activities, such as antiallergic, antihypertensive, cardiotonic, bronchodilator, antibronchitic or antitumor activity.[2] The preparation of the mentioned compounds containing a pyran and an uracil ring poses significant synthetic challenges. 3,4-Dihydro-2*H*-pyrans can be efficiently synthesized by an inverse-electron-demand hetero-Diels–Alder (HDA) reactions of α,β-unsaturated carbonyl compounds representing an 1-oxa-1,3-butadiene system with enol ethers.[3] It was stated that introducing an electron-withdrawing group in the 1-oxa-1,3-diene system can enhance their reactivity.[4] In recent work, we have shown that intermolecular and intramolecular HDA reactions are a powerful tool in 2*H*-pyran and policyclic 2*H*-pyran derivatives synthesis.[5] In this paper, the first examples of an inverse-electron demand hetero-Diels–Alder reactions of 2-cycloalkylidene-3-oxo-3-phenylpropionitriles and 5-cycloalkylidene-1,3-dimethyl-pyrimidine-2,4,6-triones as the heterodienes are described.

The Knoevenagel condensation is a common synthetic method for alkene formation.[6] The Knoevenagel reaction of various aromatic and heteroaromatic aldehydes with active methylene compounds, such as barbituric acids, Meldrum's acid, dimedone, malononitrile, ethyl cyanoacetate have been widely used in synthesis of arylidene derivatives. The reactions with aromatic aldehydes are usually catalyzed by bases or acids. Amines, such as piperidine or triethylamine, sodium ethoxide, acetic acid, or mixtures of acetic acid and sulfuric acid,[7] acetic acid and piperidine,[8] ammonium acetate and acetic acid[9] have also been successfully used as catalyst. Lewis acids, surfactants have also been employed to catalyze the condensations reactions.[10] However, reports describing analogous procedures for ketones are rare, because ketones have low reactivity in the condensations with CH acids. Soto et al. described Knoevenagel condensations of the cycloalkanones with an aryl β-ketonitrile at reflux in benzene or toluene in the

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presence of a mixture of piperidine and caproic acid as the catalyst.[11] The same reactions were carried out with using of mixture of β-alanine and acetic acid as catalyst.[12]

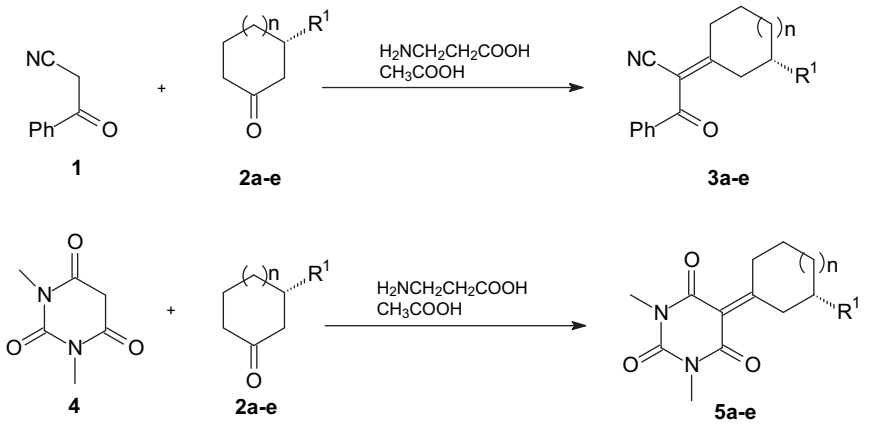
2. Results and discussion

The aim of the work was to investigate if 1-oxa-1,3-butadienes that are sterically hindered at the C-4 carbon, for example, cycloalkylidene derivatives of benzoylacetonitrile **1** or *N*,*N*′-dimethylbarbituric acid **4** can act as active heterodienes in hetero-Diels–Alder reactions in synthesis of spiro and dispirodihydropyrans. First, potential heterodienes with cycloalkylidene moiety were synthesized and in the second step their reactions with enol ethers and cyclic enol ether were conducted. Heterodienes **3a**–**e** and **5a**–**e** were synthesized by Knoevenagel condensation of benzoylacetonitrile **1** or *N*,*N*′-dimethylbarbituric acid **4** with appropriate cycloalkanone **2a**–**e** (enantiomerically pure (*R*)-(+)-3-methylcyclohexanone **2e** has been used) by refluxing in toluene or xylene for 4–6 h in the presence of β-alanine and acetic acid as catalyst according to a procedure described in ref. 12b. The progress of the reactions was monitored by TLC. Compounds **3a**–**e** and **5a**–**e** were obtained in good 77–87% yields (Scheme 1, Table 1).

Compounds **7a**–**g** and **8a**–**e** were characterized by ^{1}H, ^{13}C NMR, IR, mass spectra, and elemental analysis. The ^{1}H and ^{13}C signal assignments were confirmed by two-dimensional NMR COSY and HETCOR spectra. The configuration of the C-2′ substituents of spiropyrans **7a**–**g** or C-7′ of **8a**–**e** was assigned on the basis of ^{1}H NMR spectra. They were deduced from the chemical shift values and coupling constants of the protons attached to C-2′or C-7′ of the dihydropyran ring that exists in a half-chair conformation[13] (Table 3).

In the ^{1}H NMR spectra of spiropyrans **7a**–**g** the signals of 2′-H appear as a doublet of doublets at δ=5.13–5.28 ppm with coupling constants (^3J=7.2–8.4 and 2.4–3.0 Hz) due to coupling with two protons at C-3′ (Table 3). Thus, 2′-H is in the *axial* position and the alkoxy group occupies the *equatorial* position. (Fig. 1). The ^{1}H NMR spectra of **8a**–**e** reveal the signals of proton 7′-H as a doublet of doublets at δ=4.99–5.20 ppm with coupling constants (^3J=8.1–8.7 and 2.1–2.4 Hz) (Table 3). Thus, 7′-H is in the *axial* position and the alkoxy group is *equatorial* (Fig. 1).

For cycloadditions of compounds **3e** or **5e** with ether **6a** high diastereoselectivity was observed because products **7g** and **8e** were obtained each as one diastereoisomer from four diastereoisomers presented on the Fig. 2. Analysis of two-dimensional NMR COSY,



Scheme 1. Knoevenagel condensations of benzoylacetonitrile **1** or *N*,*N*′-dimethylbarbituric acid **4** with cyclic ketones **2a**–**e**.

Table 1
Synthesis of cycloalkylidene derivatives **3a**–**e** and **5a**–**e** by Knoevenagel condensation

Methylene compound	Cyclic ketone	*n*	R^1	Knoevenagel condensation product	Reaction time/h[a]	Yield %
1	**2a**	1	H	**3a**	5 (t)	87
1	**2b**	0	H	**3b**	4 (t)	86
1	**2c**	2	H	**3c**	5 (t)	84
1	**2d**	3	H	**3d**	6 (t)	82
1	**2e**	1	CH_3	**3e**	6 (t)	81
4	**2a**	1	H	**5a**	5 (x)	82
4	**2b**	0	H	**5b**	4 (x)	87
4	**2c**	2	H	**5c**	5 (x)	86
4	**2d**	3	H	**5d**	5 (x)	86
4	**2e**	1	CH_3	**5e**	6 (x)	77

[a] Reaction mixture was heated to reflux in toluene (t) or xylene (x).

The cycloaddition reactions of 2-cycloalkylidene-3-oxo-3-phenylpropionitriles **3a**–**e** or 5-cycloalkylidene-1,3-dimethylpyrimidine-2,4,6-triones **5a**–**e** with enol ethers **6a**–**c** were performed in toluene solution at 110 °C for 24 h and the spiropyrans **7a**–**g** and **8a**–**e** were obtained in good 78–93% yields (Scheme 2, Table 2). The progress of the reactions was monitored by TLC.

NOESY, and HETCOR spectra compounds **7g** and **8e** does not allow the configuration to be assigned unambiguously. It was impossible to determinate the crystallographic structure of compounds **7g** and **8e** because they are oils.

Although only one diastereoisomer of the compounds **7g** or **8e** was obtained in Diels–Alder reactions, the formation of the minor isomers has not been formally excluded. Therefore, acetals **7g** and **8e** were submitted to the action of Lewis acid to equilibrate one isomer to another isomer. The diastereoisomers of the compounds **7g** and **8e** obtained in the cycloaddition reactions were mixed with boron trifluoride diethyl etherate BF_3Et_2O. In both examined cases the mixtures of the diastereoisomer submitted to the action of Lewis acid (diastereoisomer **A**) and a new diastereoisomer (diastereoisomer **B**) was obtained (**A**/**B**=1:2.3 for **7g**, **A**/**B**=1:1.9 for **8e**) after 24 h at room temperature. The ratios of isomers **A**/**B** were determined on the basis of ^{1}H NMR spectra of crude mixtures after isomerization reactions.

Encouraged by previous presented results, we next embarked on the inverse-electron-demand hetero-Diels–Alder reactions between cycloalkylidene derivatives **3** or **5** and cyclic enol ether 2-methylenetetrahydropyrane **9**. The compound **9** was prepared according to the literature with a yield of 69% from 2-(chloromethyl)tetrahydropyrane[14] that was prepared from tetrahydropyran-2-methanol.[15] The cycloaddition reactions of **3a**, **3e**, **5a**,