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2-Alkoxy- and 2-alkylthio-2-alkenals in the reactions of electrophilic and nucleophilic addition. DFT study and NBO analysis

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ABSTRACT

A DFT approach at B3LYP/6-311+G** and M06/6-311+G** levels of theory, and natural bond orbital (NBO) analysis were used to investigate the electron distribution in 3-aryl(hetaryl)substituted 2-methoxy- and 2-methylthiopropenals to predict the possibility of electrophilic (Markovnikov-type) or nucleophilic (Michael-type) addition reactions depending on the nature of substituents. The dependence of the C=C bond length on the population ratio of its orbitals, $P(\pi^*_{C2=C3})/P(\pi_{C2=C3})$, was used to evaluate the donor and acceptor effects of these substituents. The changes in energy values of the frontier orbitals showed that both the electrophilic and nucleophilic abilities of the molecules studied depended on their structure. The change of the polarization direction of the double bond (calculated as the difference of the natural charges formed on its atoms) under the effect of C_β-substituent allows one to forecast the direction of the polar addition reactions for some representatives of 2-alkoxy- and 2-alkythiopropenals. The slightly different activation energies of hydration of 3-aryl(furyl)substituted 2-methoxypropenals for Markovnikov and Michael additions in acidic medium indicate to equal probability of these processes.

1. Introduction

The chemistry of unsubstituted and 2-alkylsubstituted 2-alkenals is rich and manifold. The interest in this class of compounds is provoked by both theoretical aspects of their structure,[1a–c] and their wide application for the synthesis of novel acyclic, cyclic, and heterocyclic compounds possessing valuable properties.[1d] However, the chemistry of 2-functionally substituted 2-alkenals is much less understood.[1e] Over the last decade, the possibilities for the employment of 2-substituted 2-alkenals in heterolytic 1,2- and 1,4-addition reactions as well as in diene synthesis have been intensively studied. For example, a method for the preparation of 1,4,5-trisubstituted pyrazoles from α-benzotriazolyl-α,β-unsaturated aldehydes was elaborated.[2] The Diels–Alder reaction of α-alkyl- and α-acylacroleins, prepared in situ from 5-substituted 4*H*-1,3-dioxanes, with different dienes or dienophiles allowed various adducts to be synthesized in excellent yields (80–100%).[3] The application of this strategy facilitated the total synthesis of the strained cytotoxin euplotin A.[4] Novel organic catalysts for enantioselective Diels–Alder reactions involving α-alkyl- and α-acylacroleins as dienophiles paved the route to various dienes in high yields (72–99%) and high enantiomeric excess (74–92%).[5] 2-Amidopropenals were disclosed as building blocks for the design of β-phenethylamine pharmacophores,[6,7] alkaloids such as (±)-lepadiformin,[8] (±)-fasicularin,[9] (±)-β-erythroidine, and (±)-8-oxo-β-erythroidine,[10] as well as immunodepressant FR901483.[11] The synthesis and sensorial properties of 2-alkyl-2-alkenals and their Michael adducts, 3-(acetylthio)-2-alkylalkanals, were studied to establish a ‘structure–activity’ relationship, that facilitated their identification in complex mixtures.[12] Novel methods for the preparation of 2-bromo- and 2-chloro-2-alkenals are the evidence of a renaissance of interest in the synthesis of these versatile building blocks,[13] though the high toxicity of several pesticides is likely due to the presence of these aldehydes in trace amounts.[14]

2-Alkoxy[15]- and 2-alkylthiopropenals[16] are of special interest as the starting reagents for the synthesis of pharmaceuticals. Some α-heteroatomic alkenals were found to be metabolites in human and plant tissues.[17,18] Synthetically prepared α-functionalized α,β-unsaturated carbonyl compounds serve as models of complex natural products, the transformations of which are hard to study in multi-component biological substrates.[19] Previously, it was showed that unlike unsubstituted propenal, 2-alkoxypropenals (**1**) underwent hydrolysis, alcoholysis, and hydrothiolation in acidic media according to Markovnikov[20] to afford methylglyoxal or its *O*- and *S*-acetals. These reactions are explained by the predominant

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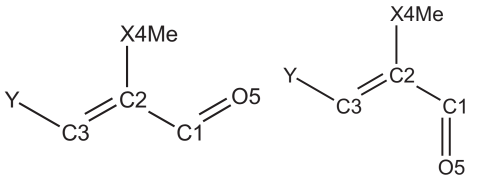
electronic effect of the OR group (as compared to the carbonyl moiety) on the double bond.



Z, s-trans *Z, s-cis*

1a-5a, **8a-15a** **1b-5b**, **8b-15b**

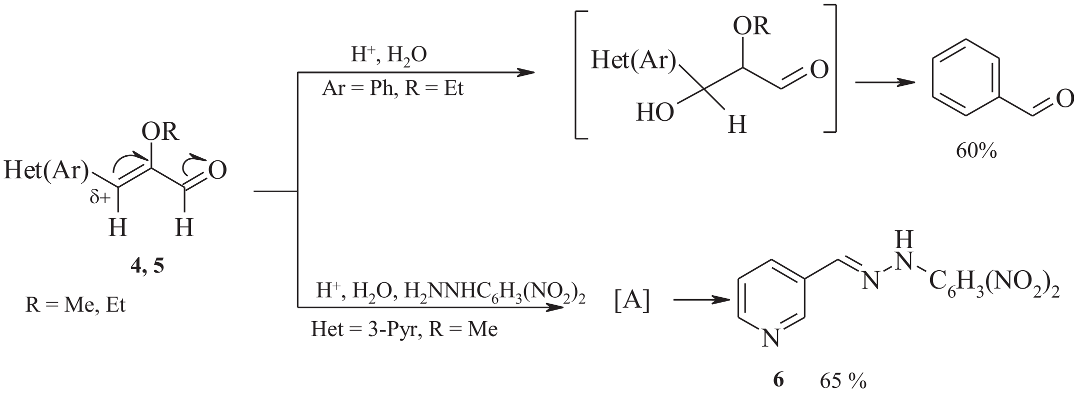
X4 = O, Y = H (**1**), Ph (**4**), 3-Py (**5**), Fur (**8**), 4-NO$_2$Ph (**12**), 2-NO$_2$Ph (**13**), 5-NO$_2$Fur (**14**);

X4 = S, Y = H (**2**), Fur (**9**), Thienyl (Th) (**10**), 3-Pyridyl (Py) (**11**), 5-NO$_2$Fur (**15**);

X4Me = OSiMe$_3$, Y = H (**3**).

Fig. 1. Stable conformers of 3-aryl(hetaryl)-2-methoxy- and 2-methylthiopropenals.

For 2-alkylthiosubstituted propenals (**2**) (Fig. 1) such reactions are not typical.[21] Unstable 2-trimethylsiloxypropenal (**3**) (Fig. 1) was hydrolyzed by air moisture across the vinyloxy group [N.A. Keiko, unpublished results]. However, the hydrolysis of 2-ethoxy-3-phenylpropenal (**4**) in acidic medium (60 °C, 1–1.5 h) furnished benzaldehyde.[22] Such a result is likely due to the primary attack of the OH^- ion at the β-atom of the double bond to generate an intermediate (Scheme 1), which further undergoes a retro-aldol reaction. The hydrolysis of 2-methoxy-3-pyridylpropenal **5**, recently synthesized by us, was accompanied by a similar transformation, the hydrazone of 2-pyridine-3-carbaldehyde **6** being isolated as the reaction product.[22] The Michael addition of water to a conjugated carbonyl compound in acid medium is very important but poorly known.[23]



Scheme 1.

The results obtained show that several 2-alkoxy-3-aryl-(hetaryl)-2-alkenals (**4**, **5**, **8**–**15**) (Fig. 1) can be employed in three directions: (i) heterolytic addition to the 1,2- or (ii) 1,4-positions (Michael-type), and (iii) 3,4-addition (Markovnikov-type). Nucleophilic 1,4-addition of *C*- and *S*-nucleophiles in an alkaline medium is also possible for 2-alkoxypropenals (**1**).[24,25]

In addition, functionalized pyrroles are known to be readily synthesized by the three-component reaction between α,β-unsaturated aldehydes, primary amines, and nitroalkanes.[26] However, an attempt to prepare 2-methyl-4-ethoxypyrroles by a protocol[26b] involving the reaction of 2-ethoxypropenal, organylamines, and nitroethane in the presence of promoters (SiO$_2$ and MWI) delivered 4-nitro-3-organylamino-2-ethoxypentanes (**7**) (Scheme 2), i.e., the nucleophilic attack was directed to the 1,2-position and was accompanied by further condensation.[27]

It was assumed that formation of the pyrrole in the three-component reaction proceeded via the initial generation of an imine. Then the nitroethane added to the latter at the 1,4-position followed by the cyclization of the intermediate product.[28]

To confirm this hypothesis, earlier we carried out the synthesis using the butylimine of 2-ethoxypropenal as a starting reagent.[27]

3-Butylamino-4-nitro-2-ethoxypentene (**7a**) turned out to be the only product of this reaction (Scheme 3). The impossibility of the1,4-addition of nitroethane was explained by the prevailing mesomeric effect of the OEt group compared to the C═NBu moiety, as well as by generation of a partially negative charge on the β-carbon.

DFT and ab initio methods were used successfully for the study of the reactivity of captodative ethylenes in polar cycloaddition reactions and the regioselectivity of the protonation of captodative trifluoromethylated enamines.[29] Such calculations, with NBO analyses, predict the regio- and stereo-selectivities of the hetero Diels–Alder reactions between 1,3-butadiene and diimides correctly.[30] NBO electron density distribution exhibits superior numerical stability over the Mulliken population analysis, and when the NBO charges were used for the carbon atom, a good correlation