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Regioselective α- and β-Addition to Alkyl Propiolates: Experimental and Theoretical Study

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In this paper, two different regioselectivity in reaction of nucleophiles with alkyl propiolates were reported. In present experiments, the reaction of NH and OH containing acids with alkyl propiolates in presence of triphenyl phosphine were studied. After determining final structure of products, it was shown that the NH acids added to the α-position and OH acids added to the β-position of alkyl propiolates. These experimentals results have been confirmed by theoretical study using *ab initio* and denisty functional methods.

Key Words: Regioselective, α- and β-Addition, Alkyl propiolates, Triphenyl phosphine.

INTRODUCTION

Nucleophilic addition to activated π-systems such as α- and β-unsaturated carbonyls is one of the oldest and most useful method in organic synthesis[1-3]. Michael reactions involved the addition of sodium diethyl malonate and sodium acetoacetate to ethyl cinnamate[4]. This new category of organic reactions was named Michael addition and consists of conjugate addition of nucleophiles to β-position of unsaturated esters. These reactions showed good advantages in formation of C-C bond, the important technique in organic synthesis[5]. The scope of these reactions was extended and many papers concerning about addition of various nucleophiles to conjugated ionones (C≡C triple bond conjugated with carbonyl group) were reported[6-8]. One of these new methods is nucleophilic addition to acetylenic esters or alkyl propiolates. Like other nucleophiles, phosphorus nucleophiles can be added to π-activated systems in Michael-type addition reaction[9-12].

The efficient method in addition of nucleophiles to alkyl propiolates and dialkyl acetylene dicarboxilates in presence of triphenyl phosphine has also been reported in the literature[13-16]. Also, addition to alkyl propiolates is more attractive than to dialkyl acetylenedicarboxylates because of probability of regioselctivity in these reactions[17,18]. In other word, α- or β-addition can

be observed in addition to alkyl propiolates while dialkyl acetylenedicarboxylates have two similar position *vs.* nucleophilic additions. Thus, the present research focussed on addition to alkyl propiolates in presence of triphenyl phosphine and the results were subjected to computational analysis.

EXPERIMENTAL

Starting materials were obtained from Fluka and Merck and were used without further purification. IR spectra were determined as KBr pellets on a Shimadzu model 470 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded using a Jeol FT-90 MHz spectrometer and a Bruker DRX-500 Avance spectrometer in $CDCl_3$ with tetramethylsilane as internal standard. Elemental analyses for C, H and N were performed using a Heraeus CHN-O-Rapid analyzer. All yields refer to isolated products after purification.

Procedure: A mixture of triphenyl phosphine (1 mmol) and NH or OH containing acid (1 mmol) in dichloromethane (20 mL) is cooled to 0 °C by ice-water bath and alkyl propiolates (1 mmol) was added drop wise at 0 °C over 10 min. Then permit the reaction mixture to reach to room temperature. After 24 h of stirring, the solvent was removed under reduced pressure and the viscous residue was purified by column chromatography (Merck silica gel 60, 230-400 Mesh ASTM) using a hexane:ethyl acetate gradient from 3:2 to 1:1. The solvent was removed under reduced pressure and pure product obtained as yellow oil. ^{1}H NMR, ^{13}C-NMR, IR spectra and elemental analysis were entirely consistent with the assigned structures. The physical and spectra data of selected compounds are as follows:

Ethyl 2-(2-acetyl-1*H*-pyrrol-1-yl)acrylate (4a): Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.02 (dd, 1H, Ar-H), 6.85 (dd, 1H, Ar-H), 6.27 (dd, 1H, Ar-H), 6.22 (s, 1H, C=CH_2), 5.64 (s, 1H, C=CH_2), 4.24 (q, *J* = 7 Hz, 2H, CH_2), 2.4 (s, 3H, C(O)Me), 1.28 (t, *J* = 7 Hz, 3H, CH_3) ppm; ^{13}C NMR (22.4 MHz, $CDCl_3$): δ = 187.6, 163.0, 139.9, 131.8, 130.4, 119.7, 118.7, 109.5, 61.4, 26.7, 14.0 ppm; IR (KBr, ν_{max}, cm^{-1}): 1729 (C=O), 1649 (C=O). Yield 78 %, m.f. $C_{12}H_{13}NO_3$.

Methyl 2-(2-acetyl-1*H*-pyrrol-1-yl)acrylate (4b): Yellow oil, ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.00 (dd, 1H, Ar-H), 6.85 (dd, 1H, Ar-H), 6.24 (dd, 1H, Ar-H), 6.18 (s, 1H. C=CH_2), 5.62 (s, 1H, C=CH_2), 3.75 (s, 3H, CH_3), 2.38 (s, 3H, C(O)Me) ppm; ^{13}C NMR (22.4 MHz, $CDCl_3$): δ = 187.5, 163.4, 139.5, 131.7, 130.3, 119.7, 118.9, 109.5, 52.2, 26.0 ppm; IR (KBr, ν_{max}, cm^{-1}): 1734 (C=O), 1649 (C=O). Yield 73 %, mf. $C_{11}H_{11}NO_3$.

Ethyl (2E)-3-({[(1E)-phenylmethylene]amino}oxy)acrylate (8a): Yellow oil; ^{1}H NMR (90 MHz, $CDCl_3$): δ = 8.25 (s, 1H, HC=N), 8.0 (d, *J* = 17 Hz, 1H, HC=C), 7.2- 7.8 (m, 5H, Ph), 5.7 (d, *J* = 17 Hz, 1H, C=CH), 4.2 (q, *J* = 9 Hz, 2H, CH_2), 1.27 (t, J = 9 Hz, 3H, CH_3) ppm; ^{13}C NMR (22.4 MHz, $CDCl_3$): δ = 182.1, 166.2, 153.8, 133.8, 131.5, 129.4, 128.8, 99.6,

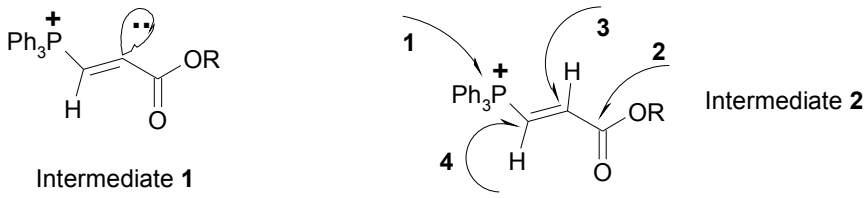
61.4, 14.3 ppm; IR (KBr, ν_{max}, cm^{-1}): 1714.0 (C=O), 1215, 1103, 1100. Yield 86 %, $C_{11}H_{13}NO_3$.

Methyl (2E)-3-({[(1E)-phenylmethylene]amino}oxy)acrylate (8b): Yellow oil; ^1H NMR (90 MHz, $CDCl_3$): δ = 8.2 (s, 1H, HC=N), 8.0 (d, *J* = 17 Hz, 1H, HC=C), 7.2-7.8 (m, 5H, Ph), 5.7 (d, *J* = 17 Hz, 1H, C=CH), 3.7 (s, 3H) ppm; ^{13}C NMR (22.4 MHz, $CDCl_3$): δ = 181.8, 166.2, 153.8, 133.8, 131.5, 129.4, 128.8, 101.4, 52.1 ppm; IR (KBr, ν_{max}, cm^{-1}): 1705 (C=O), 1628 (C-H aromatic), 1211 (C-O). Yield 84 %, $C_{10}H_{11}NO_3$.

RESULTS AND DISCUSSION

In case of the addition to alkyl propiolates, in most cases, only β-addition was observed. The other interesting aspect of these reactions is using triphenyl phosphine. In these reactions, first triphenyl phosphine added to β-position of alkyl propiolates and the dionic and basic intermediate **1** was prepared. If there is any source of acidic proton (C-H, N-H, or O-H) in the reaction vessel, this intermediate can remove this proton from its source and give intermediate **2**.

The intermediate **2** is an interesting molecule. Because when we subjected to nucleophile in the solution (these nucleophiles can be produced *in situ* from deprotonation of acid source by intermediate 1), this can attack to the intermediate **2** by four different ways as shown in **Scheme-I**.

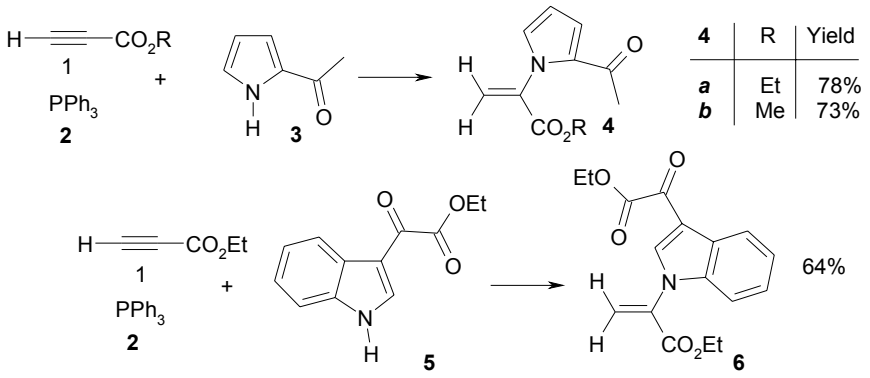


Scheme-I

The way **1** arising from electrostatic attraction and can not be observed because it can be easily rearranged or reacted again to give other products by other ways. The way **2**, is conjugate addition (1,4 or Michael-type addition) and with many nucleophiles is the major way. The way **3** is α-addition and has never observed in common reactions. But in presence of triphenyl phosphine, this addition is observed in some reactions. The way **4** is straight addition to carbonyl and only can be occurred with strong nucleophiles.

For performing these reactions, two different proton donors have been used. First, we used 2-acetyl pyrrole as a NH acid for reacting with alkyl propiolates in presence of triphenyl phosphine and mixed triphenyl phosphine and NH acid, then added drop wise alkyl propiolates and allowed the mixture to stir for 24 h. After work-up, purification of products and determination of their structures, only the α-addition product without formation of

any β-addition or other products have been obtained. For examining this regioselectivity, we use another NH acid source, ethyl-3-indolyl oxoacetate and obtain the same product, α-addition. Results of these reactions are briefly shown in **Scheme-II**.

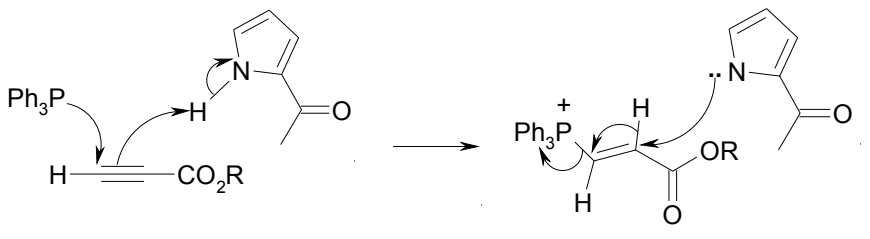


Scheme-II

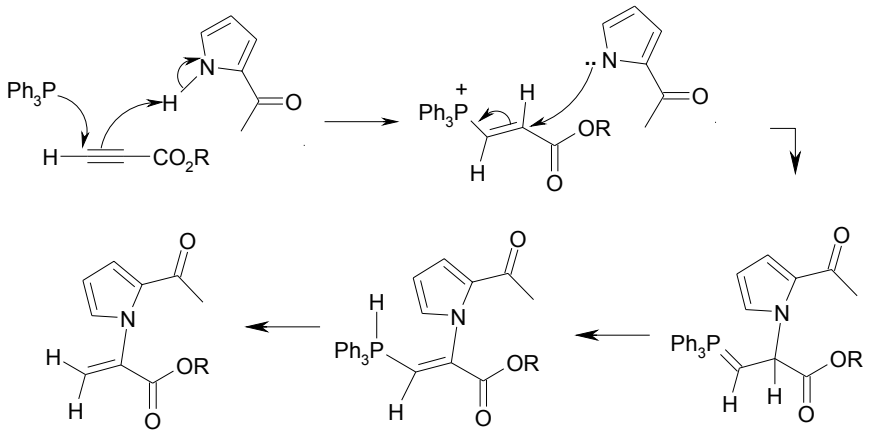
After these two reactions, it is observed that addition of NH acids to alkyl propiolates in presence of triphenyl phosphine yield the α-addition product. This compound is produced from addition of deprotonated NH acid to the α-position of intermediate **2**. In the addition step, it is interesting to note that how the triphenyl phosphine group leaves the intermediate **2** and how the nucleophile attack to it and produce final product. Two mechanisms have been proposed to explain these reactions.

In first suggestion, contemporary addition of deprotonated acid to α-position, H-shift to β-position and leaving the triphenyl phosphine group is proposed. This mechanism is shown in **Scheme-III**.

In second suggestion, deprotonated acid attack to the α-position and the π-bond between C2-C3 is migrated between C3-P and produced phosphorus ylide. Then two subsequent 1,3 and 1,2 H-shift and work-up step give the final product. All these steps shown in **Scheme-IV**.



Scheme-III

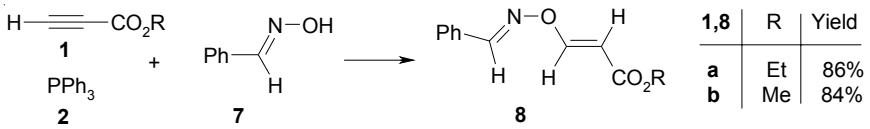


Scheme-IV

On comparing of these two mechanisms with reported experimental observations, it is suggested that the second mechanism is more reliable because it is proved that in presence of carbonyl group in this reaction, the Wittig reaction occurred[19,20]. It is obvious evidence for existence of phosphorus ylide that only prepared in the mechanism **2**.

After completing first reaction, the other acid sources in the same reaction condition have been examined. Thus, benzaldoxime is used as a source of OH acid. But unlike first reaction, only the β-addition or conjugate addition product was obtained. This type of addition is more usual than α-additions to unsaturated carbonyls. In **Scheme-V**, the results of this reaction by using benzaldoxime as a source of OH acid have been showed.

Like other conjugate addition to conjugated C=C and C=O π-systems, this mechanism is simple and clear and consists of two stages, conjugate addition and leaving the phosphine group.



1,8	R	Yield
a	Et	86%
b	Me	84%

Scheme-V

After these results, an important question is arised to solve the reason of this difference in regioselectivity. And what we don't obtained products **9** (prepared from β-addition of NH acid to alkyl propiolates) and **10** (prepared from α-addition of OH acid to alkyl propiolates). In **Scheme-VI**, it is observed that these two probable products in present reaction condition did not form.

10 **9**

Scheme-VI

As a simple reason, it seems that hardness and softness postulation can be explained these results. Nitrogen is softer nucleophile than oxygen so that, it attack to the softener position of alkyl propiolates that this position is certainly α-position. In resonance structures, positive charge is set on the β-position. So the α-position is softer than β-position, because of having less positive charge.

But, only this reason is not convincing about this regionselectivity and it is decided to use method of calculation to prove. For this purpose, Gaussian 98 program is applied. All calculations were performed using density functional theory applying the B3LYP hybrid functional and *ab initio* Hartree-Fock (HF) method as implemented in Gaussian 98 and 6-311+G* and 6-311++G** basis set was used for all atom types. Normal mode analysis was performed on the optimized geometries to determine the type of stationary points, *i.e.* minima or transition states. All energies were corrected for zero-point vibrational energy. Optimized geometries were located by minimizing energy, with respect to all geometrical coordinates and without imposing any symmetry constraints.

The PM3 results were used as input for the *ab initio* calculations, which were carried out using Hyperchem 7. Vibrational frequencies were calculated at the same level for all geometries, which were confirmed to have zero imaginary frequency. The frequencies were scaled by a suitable factor of for HF and B3LYP method and used to compute the zero point vibrational energies.

The author has optimized and calculated energy of prepared products **4b** (α-addition of NH acid) and **8b** (β-addition of OH acid) and compared them with product **9** (β-addition of NH acid) and **10** (α-addition of OH acid) but the author did not obtained these two last compounds in present reactions (**Scheme-VI**) by *ab initio* and density functional method with two different basis sets. The final results of these calculations are shown in Tables 1 and 2.

In Tables 1 and 2, it is observed that in probable products of addition of OH acids (**8b** and **10**), the β-substituted product (**8b**) is more stable (about 0.013 HF or 8 kcal/mol) than α-substituted product (**10**) or it is thermo-

TABLE-1
RESULTS OF CALCULATION FOR COMPARING COMPOUNDS **8b** WITH **10**

	Energy (HF)	ZPE	Total energy (HF)	Total energy (kcal/mol)	Energy (HF)	ZPE	Total energy (HF)	Total energy (kcal/mol)
	HF/6-311+G*				HF/6-311++G**			
8b	-702.084	0.217091	-701.891	-440437	-702.103	0.216203	-701.910	-440449
10	-702.072	0.216544	-701.879	-440429	-702.090	0.215767	-701.898	-440441
	B3LYP/6-311+G*				B3LYP/6-311++G**			
8b	-706.331	0.201611	-706.152	-443110	-706.349	0.201104	-706.170	-443122
10	-706.318	0.200872	-706.139	-443102	-706.335	0.200470	-706.157	-443114

TABLE-2
RESULTS OF CALCULATION FOR COMPARING COMPOUNDS **4b** WITH **9**

	Energy (HF)	ZPE	Total energy (HF)	Total energy (kcal/mol)	Energy (HF)	ZPE	Total energy (HF)	Total energy (kcal/mol)
	HF/6-311+G*				HF/6-311++G**			
9	-664.254	0.210819	-664.066	-416702	-664.139	0.21106	-663.951	-416629
4b	-664.255	0.210082	-664.068	-416703	-664.140	0.210309	-663.953	-416631
	B3LYP/6-311+G*				B3LYP/6-311++G**			
9	-668.261	0.195972	-668.087	-419224	-668.278	0.195432	-668.104	-419235
4b	-668.26	0.195163	-668.087	-419224	-668.278	0.194647	-668.104	-419235

dynamic product. According to this, the β-substituted product that obtained from benzaldoxime is major product. In addition of NH acid, the present calculations shows that the energy difference between α-addition product (**4b**) and β-addition product (**9**) is not only very lower that this energy in α- and β-addition products of OH acids with HF method (0.002 *vs.* 0.013 HF or 1.26 *vs.* 8.16 kcal/mol), but also in calculation with B3LYP method this energy difference is about zero. So that, the β-addition product of this case don't have any meaningful thermodynamic priority in this reaction (because both energies are the same) and it is probable that α-substituted product is major because it can be kinetic products. This reason has been studied by calculational method by previous workers[21-26]. It is suggested that the activation energy for preparation of α-substituted product is less than the same energy for β-substituted product and this product can be prepared faster because this is kinetic product. This phenomenon explained in the literature by a destabilizing interaction between the non-reacting π-orbital of alkyne and one of the lone pairs on the imido nitrogen. These studies give results in good agreement with the experimentally observed regioselectivity for addition of NH acids to alkyl propiolates.

In conclusion, the author reported a simple method for addition of NH and OH acids to alkyl propiolates in presence of triphenyl phosphine. All experiments performed under mild condition with high yield at 24 h. This reaction shows regioselectivity. With NH acids, α-addition or straight addition is observed and with OH acids β-addition or Michael addition is observed. First is kinetic product because of lower activation energy for preparing product and second is thermodynamic product because it is more stable than the other product. This regioselectivity were investigated and proved by calculational method.

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