Reactivity of unsaturated 5(4*H*)-oxazolones with Hg(II) acetate. Synthesis of methyl *N*-benzoylamino-3-arylacrylates

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ABSTRACT

An efficient and high-yield procedure to prepare methyl *N*-benzoylamino-3-arylacrylates from unsaturated (*Z*)-2-aryl-4-arylidene-5-(4*H*)-oxazolones and $Hg(OAc)_2$ in methanol is described herein. The observed reactivity of mercury(II) acetate here is different to its usual metallating behaviour, since it cleaves the unsaturated oxazolone ring without change of stereochemistry.

Keywords: 5-(4*H*)-Oxazolones; azlactone ring opening, alcoholysis; mercury(II) acetate.

INTRODUCTION

The most important reaction in the chemistry of oxazolones is the nucleophilic opening of the heterocyclic ring,[1] hydrolysis and alcoholysis of 5(4*H*)-oxazolones giving the respective *N*-acylamino acids and esters, which are used to prepare a variety of new synthetic amino

acids.[2] The use of *N*-acylamino alkyl esters as the starting α-dehydroamino acid derivatives also enable the selective formation of the corresponding isoquinolines.[3] Some esters can be used as plant growth regulators,[4] while other acrylic acid derivatives have herbicidal activity[5] or are useful intermediates for the synthesis of the antiinflammatory agents.[6] The methods used to synthesize methyl *N*-benzoylamino-3-arylacrylates include alcoholysis of 5(4*H*)-oxazolones in presence of MeONa,[7] KOH,[8] TEA,[3,9] NEt_3,[10] $P(OEt)_3$,[11] or cyclooligosaccharides.[12] In some cases, sonication has been also used to promote the nucleophilic ring opening.[13] Recently we have shown that unsaturated 5(4*H*)-oxazolones can be *ortho*-paladated to give dimers which evolve after photocycloaddition to unprecedent oxazolones.[14] Palladated oxazolones can be also regioselectively functionalized, the process leading to a series of clean products that are easy to isolate.[15] Still, certain unsaturated oxazolone substrates proved to resist to the action of different palladation agents, while for other harsher conditions[14] were needed. To extend oxazolones C-H bond activation and functionalization we focused on finding alternative milder synthetic routes involving a metal activator such as mercuriation. As it is known many aromatic substrates which refuse to react with $Pd(OAc)_2$ were derivatized using organomercury route followed by transmetallation.[16] Mercury's unique abilities to mediate organic transformations and to transfer organic ligands to different transition metal centers provide a convenient entry to different substrates, difficult to prepare using classic synthetic methods.[17] In particular $Hg(OAc)_2$ is known to attack easily aromatic compounds,[17] and gives many interesting complexes by direct mercuriation.[18] However, the increased Lewis acid character of Hg compared to Pd may induce sometime a different reactivity behavior function of metal as it was already noticed in metallation of 1,5-bis(dimethylamino)naphthalene, when $Hg(OAc)_2$ and $Pd(OAc)_2$ gave different metallated products.[19] Another example is 3,4,5-trimethoxybenzaldehyde which does not react with $Pd(OAc)_2$ but it is easily mercuriated in the presence of mercury(II) acetate.[20] To our knowledge, the treatment of unsaturated oxazolones with mercuric derivatives has not been investigated until now, therefore we

report here the reactivity of 5(4*H*)-oxazolones towards mercury(II) acetate.

RESULTS AND DISCUSSION

With this aim we prepared (*Z*)-2-phenyl-4-arylidene-5(4*H*)-oxazolones **1a-e** according to known literature procedures (**Equation 1**).[9] Two geometric isomers are possible for **1a-e**, but the Erlenmeyer synthesis proceeds stereoselectively, favoring the thermodynamically more stable (*Z*) isomer.[21] Arguments are based on NMR studies,[22] chromatographic behavior[23] and previous X-ray determinations of molecular structures of related oxazolones.[24] With azlactones **1a-e** in hand, the next step was the study of their reactivity towards $Hg(OAc)_2$ in methanol, being known that different C,*N*-complexes have been prepared in these conditions.[18] Therefore, substrate **1a**[25] was refluxed in methanol in the presence of equimolar quantities $Hg(OAc)_2$. However, after workup only 2-benzoylamino-3-phenylmethylacrylate **2a**[26] was isolated in a very good 98% yield (**Equation 1**). The presence of the expected metallated product could not be detected.

Equation 1

The same reaction occurred when oxazolones **1b**[27] and **1c**[28] were treated with $Hg(OAc)_2$, since ester derivatives **2b** and **2c**[29] (**Table I**) were obtained in high yields. (*Z*)-2-phenyl-4(4-methoxybenzylidene)-5(4*H*)-oxazolone **1d**[30] afforded, after treatment with $Hg(OAc)_2$, 2-benzoylamino-3-(4-methoxyphenyl)methyl acrylate **2d**.[31] It is evident that in these processes the $Hg(OAc)_2$ did not behave as a metallation agent, but hydrolysed the oxazolone ring affording methyl *N*-benzoylamino-3-arylacrylates **2a-d**. Curiously the electron activated substrate **1e**[32] could not be hydrolyzed in the above conditions even if the reaction time was increased to 24 hours. In addition, even it is widely accepted that the mercuriation occurs mainly through an electrophilic substitution S_EAr pathway[33] no metallating product was detected after workup when activated substrate **1e** was employed.

It should be noted that compound **1a** remained practically unchanged when refluxed in methanol alone for 20 hrs, as noted also by Shabana et al.[11] Under the same reaction conditions $Pd(OAc)_2$ leave the oxazolone ring intact as we observed in our initial attempts to get cyclopalladated derivatives.[15] In order to see if the reaction can be catalytically driven **1d** was refluxed in MeOH using 3% molar of $Hg(OAc)_2$. However, the observed conversion of **1d** into **2d** was only (***%) after more than 36 hours.

Table I

In the ^1H NMR spectrum of **2d**, the shielding of the aromatic protons shows that the delocalization of the electron density occurs in a lower extent in comparison with starting oxazolone. The presence of a broad peak around 7.70 ppm, in **2d**, assigned to the acidic proton from the NH group is in keeping with the oxazolone cleavage. In the aliphatic area of the spectrum the existence of the methyl ester group is confirmed by a sharp peak at δ 3.79 ppm. Methyl *N*-benzoylamino-3-arylacrylates **2a-d** have been also characterized using IR spectroscopy. Absorptions assigned to the stretch of the C=O group were detected at about 1700 cm^{-1}, shifted to lower energy in all studied cases with respect to the two-component band appearing in the 1740-1780 cm^{-1} region in starting oxazolones.[14] Bands due to NH vibrations appear around 3300 cm^{-1} in products **2a-d** while the C=N stretching vibration appear at 1652 cm^{-1}. Mass spectra performed on compounds **2a-d** are strongly in the favor of the drawn structures. When compound **2b** is analyzed under MS-ES conditions the protonated molecule is detected at *m/z* 359.9, 361.8, while the cationic $[MNa]^+$ species appear at *m/z* 381.8, 383.8.

The structure of 2-benzylamino-3-(4-chlorophenyl)methyl acrylate (**2c**) was also confirmed by the determination of its molecular structure by X-ray diffraction methods. From the structure of **2c** it is obvious the cleavage of the heterocyclic ring and the incorporation of a methanol molecule (**Figure 1**). In comparison with starting oxazolones **1a-d**, which are planar,[24] the molecule planarity is destroyed by the ring opening. The crystal structure of **2c**

displays a *Z* configuration about the C8C9 double bond. This is the same configuration than that found in the oxazolone **1c**, this meaning that the reaction occurs with stereochemical retention of the configuration.

Figure 1

The molecular conformation is stabilized by an intramolecular and several intermolecular hydrogen bonds. The intramolecular H-bonds are formed between the proton on the aromatic bond C13H13 and the N1 atom [H13A···N1 2.5266 (14) Å] and has similar parameters to those found in isobutyl *N*-benzoylamino-3-(4-chlorophenyl) acrylate[34] and *N*-benzoylamino-3-(4-chlorophenyl) acrylic acid.[35] In addition to that, intermolecular H-bonds involving the aromatic CH groups, carbonyl O atoms, Cl atoms of the chlorophenyl groups and NH protons also stabilize the molecule.

In conclusion we observed that reaction of unsaturated 5(4*H*)-oxazolones with $Hg(OAc)_2$ in methanol did not lead to any metallated product. Instead mercury(II) acetate showed low Lewis acid behavior when reacted with unsaturated oxazolones. In the given reaction conditions oxazolone ring was cleaved, methyl *N*-benzoylamino-3-arylacrylates being obtained in high yields. The reaction did not occur in catallitic amounts of mercury(II) acetate while electron activated substrates could not be hydrolyzed.

EXPERIMENTAL

Chemicals of commercial grade were used without further purification. ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra were recorded in $CDCl_3$, at room temperature, on a Bruker Avance 400 spectrometer (δ in ppm, *J* in Hz) at ^{1}H operating frequency of 400.13 MHz. ^{1}H and ^{13}C NMR spectra were referenced using the solvent signal as internal standard. MS-ES mass spectra were recorded using an Esquire 3000 ion-trap mass spectrometer (Bruker Daltonic GmbH) equipped with a standard ESI/APCI source. Infrared spectra (4000-380 cm^{-1}) were recorded

on a Perkin-Elmer Spectrum One IR spectrophotometer, using nujol mulls between polyethylene sheets. Data collection was performed at room temperature on an Oxford Diffraction Xcalibur2 diffractometer using graphite-monocromated Mo-Kα radiation (λ = 0.71073 Å). An hemisphere of data was collected based on three ω-scan or φ-scan runs. The diffraction frames were integrated using the program CrysAlis RED[36] and the integrated intensities were corrected for absorption with SADABS.[37] *Structure Solution and Refinement*. The structure was solved and developed by Patterson and Fourier methods.[38] All non-hydrogen atoms were refined with anisotropic displacement parameters. The hydrogen atoms were placed at idealized positions and treated as riding atoms. Each hydrogen atom was assigned an isotropic displacement parameter equal to 1.2 times the equivalent isotropic displacement parameter of its parent atom. The structure was refined to F_o^2, and all reflections were used in the least-squares calculations.[39] Elemental analyses (CHNS) were carried out on a Perkin-Elmer 2400-B microanalyser.

Synthesis of the starting compounds

Unsaturated 5-(4*H*)-oxazolones **1a**,[25] **1b**,[27] **1c**,[28] **1d**[30] and **1e**[32] were previously prepared and characterised before. Also alcoholysis products **2a**,[26], **2c**[29] and **2d**[31] have been also spectroscopically characterised elswere.

General Procedure for preparation of methyl *N*-benzoylamino-3-arylacrylates

(*Z*)-2-Arylidene-4-phenyl-5(4*H*)-oxazolone (1.0 equiv) and mercury(II) acetate (1.0 equiv) were added in MeOH (10-30 mL). The mixture was heated for 3 to 4 hours at 70 ^{o}C until the monitoring of the reaction using TLC showed completion and then allowed to cool at room temperature. The solvent was evaporated and the residue was purified on a chromatographic column (Ethyl Acetate) to give **2a-d**.

Synthesis of methyl *N*-benzoylamino-3-(2-bromophenyl)acrylate

(*Z*)-2-(2-Bromobenzylidene)-4-phenyl-5(4*H*)-oxazolone **1b** (1.27 g, 3.89 mmol) and mercury(II) acetate (1.24 g, 3.89 mmol) were added in MeOH (30 mL). The mixture was heated for 3 hours at 70 ^{o}C and after reaction completion monitored on TLC, allowed to cool at room temperature. The solvent was evaporated to dryness and then the solid washed

three times with cold diethyl ether. The united ether phases were evaporated to give **2b** as a white solid (Yield 1.34 g, 96%). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm: 3.85 (s, 3H, COOCH$_3$), 7.12 (td, ^{3}J = 7.7 Hz, ^{4}J = 1.7 Hz, 1H, H$_{4''}$), 7.18 (t, ^{3}J = 6.8 Hz, 1H, H$_{5''}$), 7.39 (t, ^{3}J = 7.6 Hz, 2H, H$_{3'}$, H$_{5'}$), 7.47 (m, *2*H, H$_{4'}$, H$_{6''}$), 7.52 (s, 1H, H$_{7''}$), 7.57-7.62 (dd, ^{3}J = 8.0 Hz, ^{4}J = 1.2 Hz, 1H, H$_{3''}$), 7.77 (d, ^{3}J = 7.4 Hz, 2H, H$_{2'}$, H$_{6'}$), 7.97 (broad s, 1H, NH). ^{13}C NMR (101 MHz, *CDCl$_3$*) δ ppm: 52.84 (1C, COO<u>C</u>H$_3$), 124.34, 126.06, 133.21, 134.54 (4C, C$_{1''}$, C$_{2''}$, C$_{1'}$, C$_{2}$), 127.14 (1C, C$_{5''}$), 127.33 (2C, C$_{2'}$, C$_{6'}$), 128.56 (2C, C$_{3'}$, C$_{5'}$), 129.34, 129.37 (2C, C$_{4'}$, C$_{7''}$), 130.09 (1C, C$_{4''}$), 132.07 (1C, C$_{6''}$), 132.83 (1C, C$_{3''}$), 165.38, 165.43 (2C, CO, <u>C</u>OOCH$_3$). MS-ES *m/z*: 359.9, 361.8 [MH]$^{+}$, 381.8, 383.8 [MNa]$^{+}$. Anal. Calc. for C$_{17}$H$_{14}$BrNO$_3$: C, 56.69; H, 3.92; N, 3.89. Found: C, 56.84; H, 3.76; N, 3.56.

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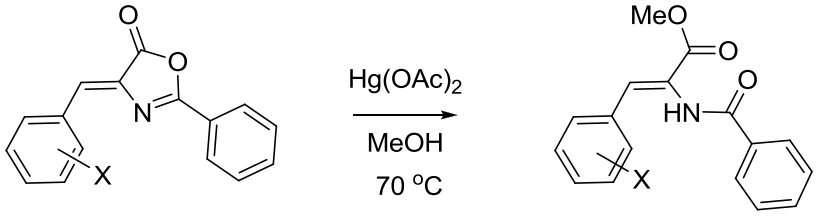
Equation 1



1

X = H (**1a**),
2-Br (**1b**),
4-Cl (**1c**),
4-OMe (**1d**),
3,4-OMe (**1e**)

2

X = H (**2a**),
2-Br (**2b**),
4-Cl (**2c**),
4-OMe (**2d**)

Table I. Alcoholysis of (*Z*)-2-aryl-4-arylidene-5(4*H*)-oxazolones **1a-d**.

Oxazolone	X	Product	Yield %
1a	H	**2a**	98
1b	2-Br	**2b**	96
1c	4-Cl	**2c**	97
1d	4-OMe	**2d**	94
1e	3,4-OMe	-	-

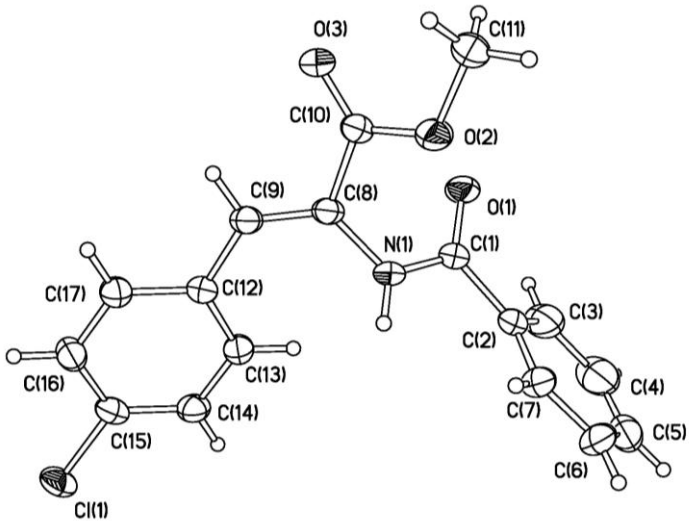


Figure 1. ORTEP plot of **2c** with thermal ellipsoids drawn at the 50% probability level

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