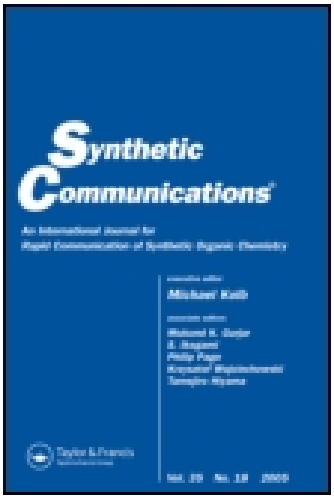

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REACTIVITY OF UNSATURATED 5(4*H*)-OXAZOLONES WITH Hg(II) ACETATE: SYNTHESIS OF METHYL *N*-BENZOYLAMINO-3-ARYLACRYLATES

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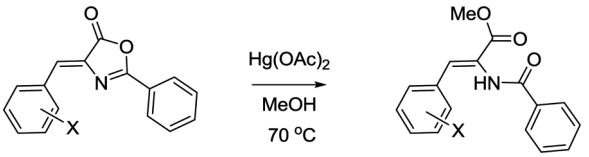
GRAPHICAL ABSTRACT



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 than its usual metallating behavior and it cleaves the unsaturated oxazolone ring without change of stereochemistry.*

Keywords Alcoholysis; azalactone ring opening; mercury(II) acetate; 5-(4*H*)-oxazolones

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, which gives 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 enables the selective formation

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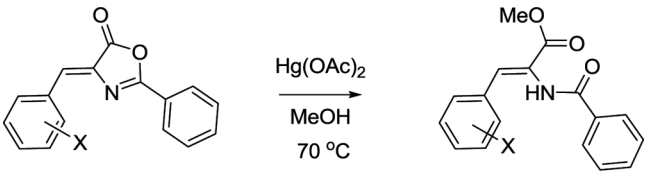
of the corresponding isoquinolines.[3] Some esters can be used as plant growth regulators,[4] while other acrylic acid derivatives have herbicidal activity[5] or are useful intermediates for the synthesis of anti-inflammatory agents.[6] The methods used to synthesize methyl *N*-benzoylamino-3-arylacrylates include alcoholysis of 5(4*H*)-oxazolones in the presence of MeONa,[7] KOH,[8] triethylamine (TEA),[3,9] NEt_3,[10] $P(OEt)_3$,[11] and 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, which leads to a series of clean products that are easy to isolate.[15] Still, certain unsaturated oxazolone substrates resisted the action of different palladation agents, while for others, harsher conditions[14] were needed. To extend oxazolone C-H bond activation and functionalization, we focused on finding milder synthetic routes involving a metal activator such as mercuriation. Many aromatic substrates that refuse to react with $Pd(OAc)_2$ were derivatized using an 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 that are 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 sometimes may induce a different reactivity behavior of metal, as 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 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, and therefore we report here the reactivity of 5(4*H*)-oxazolones toward 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 (Scheme 1).[9] Two geometric isomers



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**)

Scheme 1. Synthesis of methyl *N*-benzoylamino-3-arylacrylates.

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 toward $Hg(OAc)_2$ in methanol, because it was 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 of $Hg(OAc)_2$. However, after workup, only 2-benzoylamino-3-phenylmethylacrylate **2a**[26] was isolated in 98% yield (Scheme 1). The presence of the expected metallated product could not be detected.

The same reaction occurred when oxazolones **1b**[27] and **1c**[28] were treated with $Hg(OAc)_2$, because ester derivatives **2b** and **2c**[29] (Table 1) were obtained in good 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 hydrolyzed the oxazolone ring, affording methyl *N*-benzoylamino-3-arylacrylates **2a–d**. Curiously, the electron-activated substrate **1e**[32] could not be hydrolyzed in these conditions even if the reaction time was increased to 24 h. In addition, it is widely accepted that the mercuriation occurs mainly through an electrophilic substitution S_EAr pathway,[33] but 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 hs, as noted also by Shabana et al.[11] Under the same reaction conditions, $Pd(OAc)_2$ leaves the oxazolone ring intact, as we observed in our initial attempts to get cyclopalladated derivatives.[15] To see if the reaction can be catalytically driven, **1d** was refluxed in MeOH using 3 mol% of $Hg(OAc)_2$. However, the observed conversion of **1d** into **2d** was only 12% after more than 36 h.

In the ^1H NMR spectrum of **2d**, the shielding of the aromatic protons shows that the delocalization of the electron density occurs to a lesser 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 infrared (IR) spectroscopy. Absorptions assigned to the stretch of the C=O group were detected at about 1700 cm^{-1}, and 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

Table 1. 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	—	—

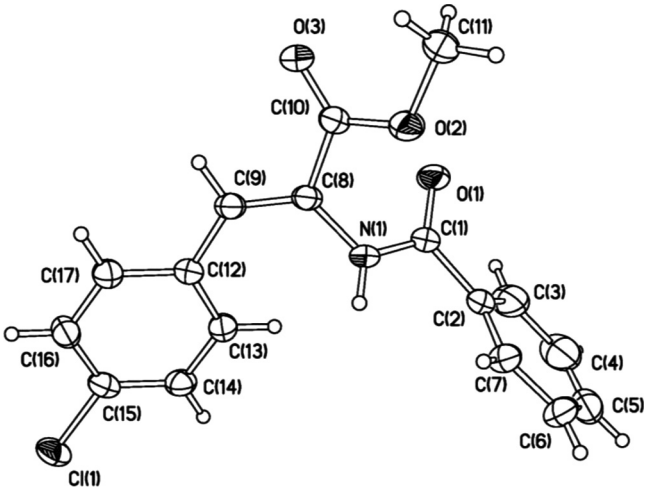


Figure 1. ORTEP plot of **2c** with thermal ellipsoids drawn at the 50% probability level.

around 3300 cm^{-1} in products **2a–d** while the C=N stretching vibration appears 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 mass spectrometry–electrospray ionization (MS-ES) conditions, the protonated molecule is detected at m/z 359.9 and 361.8, while the cationic $[MNa]^+$ species appear at m/z 381.8 and 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**, the cleavage of the heterocyclic ring and the incorporation of a methanol molecule (Fig. 1) is obvious. 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 as that found in the oxazolone **1c**, meaning that the reaction occurs with stereochemical retention of the configuration.

The molecular conformation is stabilized by an intramolecular and several intermolecular hydrogen bonds (Table 2). The intramolecular H-bonds are formed

Table 2. Hydrogen-bonding geometry (Å, °)

D-H···A	D-H	H···A	D···A	D-H···A
C13-H13A···N1	0.9296(16)	2.5266(14)	3.0942(22)	119.686(103)
C6-H6A···Cl1[a]	0.9302(29)	3.1497(5)	3.9372(24)	143.592(155)
C14-H14A···Cl1[b]	0.9304(14)	3.0643(5)	3.5805(18)	116.725(97)
N1-H1A···O1[b]	0.8603(14)	1.9868(10)	2.8278(18)	165.459(102)
C17-H17A···O3[c]	0.9303(14)	2.539(1)	3.3020(17)	139.482(99)
C9-H9A···O3[c]	0.9301(14)	2.6324(11)	3.4668(19)	149.623(103)
C11-H11A···O2[c]	0.9604(21)	2.6193(13)	3.4707(23)	147.902(124)

[a] 1 − x, 2 − y, 1 − z.
[b] 1 + x, 1 + y, z.
[c] 2 + x, 1 + y, z.

between the proton on the aromatic bond C13H13 and the N1 atom [H13A···N1 2.5266 (14) Å] and have parameters similar to those found in isobutyl *N*-benzoylamino-3-(4-chlorophenyl) acrylate[34] and *N*-benzoylamino-3-(4-chlorophenyl) acrylic acid.[35] In the structure, Cl atom forms weak C-H···Cl hydrogen bonds [C6-H6A···Cl1 3.1497(5) Å respectively C14-H14A···Cl1 3.0643(5) Å] that are shorter than the sum of the Van der Waals radii of carbon and chlorine (3.60 Å).[36] A closer check of the crystal structure revealed further N-H···O intermolecular interactions [N1-H1A···O1 1.9868(10) Å], with the N1-H1A···O1 angle tending to be close to linear [165.459(102)]. In addition to this, the C-H···O interactions [C17-H17A···O3 2.539(1) Å, C11-H11A···O22.6193(13) Å, and C9-H9A···O3 2.6324(11) Å] are also stabilizing the structure.

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, the oxazolone ring was cleaved and methyl *N*-benzoylamino-3-arylacrylates were obtained in good yields. The reaction did not occur in catalytic amounts of mercury(II) acetate while electron-activated substrates could not be hydrolyzed.

EXPERIMENTAL

Chemicals of commercial grade were used without further purification. ^1H and $^{13}C\{^1H\}$ NMR spectra were recorded in $CDCl_3$, at room temperature, on a Bruker Avance 400 spectrometer (δ in ppm, *J* in Hz) at ^1H operating frequency of 400.13 MHz. ^1H 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). A hemisphere of data was collected based on three ω-scan or φ-scan runs. The diffraction frames were integrated using the program CrysAlis RED,[37] and the integrated intensities were corrected for absorption with SADABS.[38]

Structure Solution and Refinement

The structure was solved and developed by Patterson and Fourier methods.[39] All nonhydrogen 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.[40] Elemental analyses were carried out on a Perkin-Elmer 2400-B microanalyzer.

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 characterized. Also, alcoholysis products **2a**,[26] **2c**,[29] and **2d**[31] have been spectroscopically characterized elsewhere.

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 h at 70 °C until the monitoring of the reaction using thin-layer chromatography (TLC) showed completion and then was 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 h at 70 °C and, after reaction completion as shown by TLC, allowed to cool at room temperature. The solvent was evaporated to dryness, and then the solid was 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, $COO\underline{C}H_3$), 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, $\underline{C}OOCH_3$). 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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