# Direct heterocyclization of [3,4-dihydroisoquinolin-1(2*H*)-ylidene]acetamides with aroylketenes. Crystal and molecular structure of (*Z*)-3-(4a-methyl-1,3,4,4a,5,10b-hexahydrophenanthridin-6(2*H*)-ylidene)-4-phenylpyridine-2,6(1*H*,3*H*)-dione

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**Abstract**
Aroylketenes generated by thermolysis of 6-aryl-2,2-dimethyl-4*H*-1,3-dioxin-4-ones react with (*Z*)-2-[3,3-dimethyl-3,4-dihydroisoquinolin-1(2*H*)-ylidene]acetamides and (*Z*)-2-[4a-methyl-1,3,4,4a,5,10b-hexahydrophenanthridin-6(2*H*)-ylidene]acetamide to produce (*Z*)-4-aryl-3-(3,3-dimethyl-3,4-dihydroisoquinolin-1(2*H*)-ylidene)pyridine-2,6(1*H*,3*H*)-diones and (*Z*)-3-(4a-methyl-1,3,4,4a,5,10b-hexahydrophenanthridin-6(2*H*)-ylidene)-4-phenylpyridine-2,6(1*H*,3*H*)-dione. The crystal and molecular structure of (*Z*)-3-(4a-methyl-1,3,4,4a,5,10b-hexahydrophenanthridin-6(2*H*)-ylidene)-4-phenylpyridine-2,6(1*H*,3*H*)-dione was confirmed by X-ray analysis.

**Keywords:** Aroylketene, dioxinone, [3,4-dihydroisoquinolin-1(2H)-ylidene]acetamide, hetero cyclization

## Introduction

5-Arylfuran-2,3-diones are known to undergo a thermal decarbonylation with generation of aroylketenes[1,2] which can readily participate in the intermolecular cycloaddition reactions[3,4] and can acylate weak nucleophiles to give aroylacetyl derivatives[3,5]. At the same time 5-arylfuran-2,3-diones themselves can acylate nucleophiles yielding aroylpyruvoyl derivatives under the temperatures lower than required for the process of aroylketenes generation[3,6]. Recently we have described the interaction of 5-arylfuran-2,3-diones with substituted [3,4-dihydroisoquinolin-1(2*H*)-ylidene]acetamides giving rise to (3*E*,5*Z*)-5-(2-aryl-2-

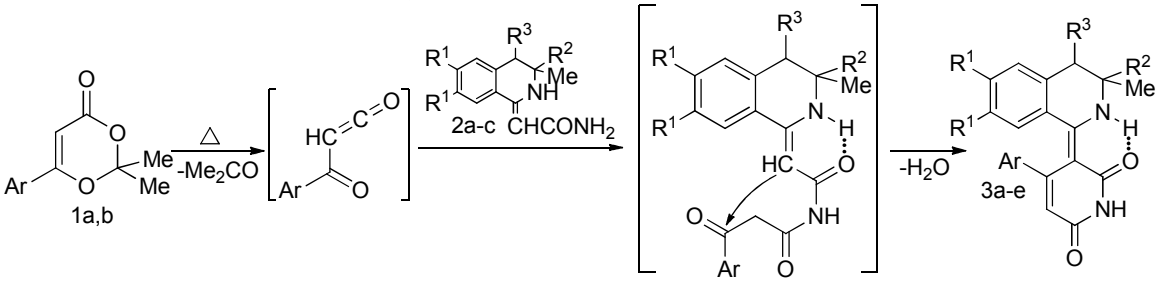
 

oxoetyliden)-3-(3,3-dimethyl-3,4-dihydroisoquinolin-1(2*H*)-ylidene)pirrolydin-2,4-diones which structures were confirmed by X-ray analysis[7]. It is known that 6-aryl-2,2-dimethyl-4*H*-1,3-dioxin-4-ones[8] – the products of aroylketenes [4+2]-cycloaddition reaction to the acetone carbonyl group, can undergo the thermal retro-Diels–Alder reaction thus acting as the source of aroylketenes[9].

In the course of our studies on interaction of dioxoheterocycles and heterocumulenes derived from them with enamines of the isoquinoline series, we have examined some reactions of 6-aryl-2,2-dimethyl-4*H*-1,3-dioxin-4-ones with substituted [3,4-dihydroisoquinolin-1(2*H*)-ylidene]acetamides.

## Results and Discussion

6-Aryl-2,2-dimethyl-4*H*-1,3-dioxin-4-ones **1a,b** interaction with (*Z*)-2-[3,3-dimethyl-3,4-dihydroisoquinolin-1(2*H*)-ylidene]acetamides **2a,b** and (*Z*)-2-[4a-methyl-1,3,4,4a,5,10b-hexahydrophenanthridin-6(2*H*)-ylidene]acetamide **2c** proceeding at a 1:1 molar ratio of reactants under reflux for 2-4 h in anhydrous toluene (TLC control) resulted in formation of (*Z*)-4-aryl-3-(3,3-dimethyl-3,4-dihydroisoquinolin-1(2*H*)-ylidene)pyridine-2,6(1*H*,3*H*)-diones **3a-d** and (*Z*)-3-(4a-methyl-1,3,4,4a,5,10b-hexahydrophenanthridin-6(2*H*)-ylidene)-4-phenylpyridine-2,6(1*H*,3*H*)-dione **3e**, correspondingly (Scheme 1). The structure of compound **3e** was confirmed by X-ray analysis (Figure 1).




**1**: Ar = Ph (a), $C_6H_4Me$-*n* (b); **2**: $R^1 = R^3 = H$, $R^2 = Me$ (a), $R^1 = OMe$, $R^2 = Me$, $R^3 = H$ (b), $R^1 = H$, $R^2+R^3 = (CH_2)_4$ (c); **3**: $R^1 = R^3 = H$, $R^2 = Me$, Ar = Ph (a), Ar = $C_6H_4Me$-*n* (b), $R^1$ = OMe, $R^2 = Me$, $R^3 = H$, Ar = Ph (c), Ar = $C_6H_4Me$-*n* (d), $R^1 = H$, $R^2+R^3 = (CH_2)_4$, Ar = Ph (e)

**Scheme 1.** Interaction of dioxinones **1a,b** with acetamides **2a-c**.

Compounds **3a-e** are the yellow crystal substances readily soluble in dimethylsulfoxide (DMSO) and dimethylformamide (DMF), hardly soluble in alcohols, ethers, chlorocarbons, aromatics and insoluble in saturated hydrocarbons and water.

The molecular structures of compounds **3a-e** were confirmed with the help of spectral and analytical data. For example, the IR spectra of **3a-e** contain stretching bands of a pyridinone NH-group and isoquinoline NH-group involved in the intramolecular hydrogen bonding (IHB) as broadened bands in a range 3100–3125 $cm^{-1}$, the stretching bands of a $C^6$=O lactam

carbonyl group at 1647-1655 $cm^{-1}$ and the stretching bands of a $C^2$=O carbonyl group involved in IHB at 1615-1619 $cm^{-1}$.

Analysis of compounds **3a**-**e** $^1$H NMR spectra (DMSO-$d_6$) has show that besides the signals inherent to the protons of aromatic rings and the substituents attached thereto, the spectra exhibited a singlet at δ 0.70 ppm due to three protons of the $C^{4a}$ methyl group (the isoquinoline fragment, compound **3e**), a complex multiplet at δ 1.38-2.32 ppm appeared due to eight protons of a cyclohexyl moiety $(CH_2)_4$ (compound **3e**), a singlet at δ 1.19–1.28 ppm due to six protons of two geminal methyl groups at $C^3$-atom of the isoquinoline moiety (compounds **3a-d**), a singlet at δ 2.97–3.06 ppm due to the methylene protons at $C^4$-atom of the isoquinoline moiety (compounds **3a-d**), a singlet at δ 5.51–5.59 ppm due to the vinylic protons, and two downfield singlets at 10.63–10.88 ppm and 11.78–12.08 ppm due to the NH protons of the isoquinoline and pyridine fragments , respectively.

According to the semiempirical AM1 (package Hyperchem 8.0) quantum-chemical calculations [3,4-dihydroisoquinolin-1 (2H)-ylidene]acetamides we have carried out, the most favorable nucleophilic reaction center is the acetamide group $NH_2$ (-0.404), but not the group β-CH of enamine fragment (-0.065). This explains the fact that the first step of the interaction being discussed is the amino group $NH_2$ acylation of acetamides **2a-c** by the aroylketenes followed by intramolecular cyclization with elimination of water molecule.

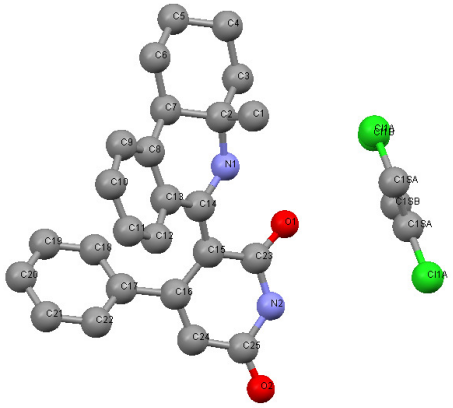


**Figure 1.** The molecular structure of (*Z*)-3-(4a-methyl-1,3,4,4a,5,10b-hexahydrophenanthridin-6(2*H*)-ylidene)-4-phenylpyridine-2,6(1*H*,3*H*)-dione **3e** in thermal ellipsoids of 50% probability.

**Crystallographic data.** According to X-Ray data compound **3e** is crystallized in centrocymmetric space group of triclinic system as solvate with 1,2-dichloroethane molecule (2:1). The solvate is placed in a private position and is disordered into two positions with coefficients of occupancy 0.5. Conformation of heterocyclic molecule is ordered by intramolecular H-bond $N^1$-H…$O^1$ and molecular packing is characterized by presence "dimeric" intramolecular H-bonds $N^2$-H…$O^2$ [3-x 1-y 1-z].

## Conclusions

The described interaction may be regarded as an example of the synthetic way to a stereoregular ensemble of two different polyfunctional heterocyclic systems and at the same time it is an example of a direct hetarylideneacetamides heterocyclization with the help of aroylketenes.

## Experimental Section

**General.** The IR spectra were recorded in mineral oil on a IFS 66 (Bruker) spectrophotometer. The $^1$H NMR Spectra were recorded at 400.1 MHz on a Bruker AM-400 instrument with dimethylsulfoxide (DMSO-*d*6) as solvent and TMS as internal standard [for compounds **3a-d**] and at 300 MHz on a Mercury-300BB instrument with dimethylsulfoxide (DMSO-*d*6) as solvent and HMDS as internal standard [for compound **3e**]. Elemental analyses for C, H and N were obtained using a LECO CHNS-932 analyzer.

**General synthetic procedure, exemplified by (*Z*)-3-(3,3-dimethyl-3,4-dihydroisoquinolin-1(2*H*)-ylidene)-4-phenylpyridine-2,6(1*H*,3*H*)-dione (3a).** A solution of compounds **Ia** (1 mmol) and **IIa** (1 mmol) in dry toluene (30 ml) was heated under reflux for 4 h and then allowed to cool. The resulted solid precipitate was filtered off and purified by recrystallization from ethanol.

**3a.** Yellow crystals (from EtOH), yield 89 %, mp 119-121 °C; IR mineral oil ($\nu_{max}$, cm$^{-1}$): 3120 w (NH), 1647 (C$^6$=O), 1617 (C$^2$=O in IHB). $^1$H NMR (400.1 MHz, DMSO-*d*$_6$): δH 1.19 (6H, s, 2CH$_3$), 2.97 (2H, s, C$^4$H$_2$), 5.55 (1H, s, CH), 6.77-7.51 (9H$_{arom}$, m, 9CH), 10.79 (1H, s, NH, isoquinilin), 12.08 (1H, s, NH, pyridine). Anal. Calcd for $C_{22}H_{20}N_2O_2$ (344.15): C, 76.72; H, 5.85; N, 8.13%. Found: C, 76.57; H, 5.97; N, 8.00%.

**(*Z*)-3-(3,3-dimethyl-3,4-dihydroisoquinolin-1(2*H*)-ylidene)-4-(4-tolyl)pyridine-2,6(1*H*,3*H*)-dione (3b).** Yellow crystals (from EtOH), yield 87 %, mp 140-142 °C; IR mineral oil ($\nu_{max}$, cm$^{-1}$): 3125 w (NH), 1648 (C$^6$=O), 1615 (C$^2$=O in IHB). $^1$H NMR (400.1 MHz, DMSO-*d*$_6$): δH 1.19 (6H, s, 2CH$_3$), 2.39 (3H, s, C$_6$H$_4$CH$_3$-p), 2.97 (2H, s, C$^4$H$_2$), 5.53 (1H, s, CH), 6.80-7.87 (8H$_{arom}$, m, 8CH), 10.75 (1H, s, NH, isoquinilin), 12.08 (1H, s, NH, pyridine). Anal. Calcd for $C_{23}H_{22}N_2O_2$ (358.17): C, 77.07; H, 6.19; N, 7.82%. Found: C, 77.06 ; H,6.39; N, 7.64%.

**(*Z*)-3-(3,3-dimethyl-6,7-dimethoxy-3,4-dihydroisoquinolin-1(2*H*)-ylidene)-4-phenylpyridine-2,6(1*H*,3*H*)-dione (3c).** Yellow crystals (from EtOH), yield 90 %, mp 132-134 °C; IR mineral oil ($\nu_{max}$, cm$^{-1}$): 3120 w (NH), 1655 (C$^6$=O), 1618 (C$^2$=O in IHB). $^1$H NMR (400.1 MHz, DMSO-*d*$_6$): δH 1.28 (6H, s, 2CH$_3$), 3.06 (2H, s, C$^4$H$_2$), 3.60 (3H, s, OCH$_3$), 3.70 (3H, s, OCH$_3$), 5.56 (1H, s, CH), 6.54 (1H$_{arom}$, s, CH), 6.71 (1H$_{arom}$, s, CH), 6.78-7.98 (5H$_{arom}$, m, 5CH), 10.68 (1H, s, NH, isoquinilin), 11.83 (1H, s, NH, pyridine). Anal. Calcd for $C_{24}H_{24}N_2O_4$ (404.17): C, 71.27; H, 5.98; N, 6.93%. Found: C, 71.21; H, 5.98; N, 6.76%.

**(*Z*)-3-(3,3-dimethyl-6,7-dimethoxy-3,4-dihydroisoquinolin-1(2*H*)-ylidene)-4-(4-tolyl)pyridine-2,6(1*H*,3*H*)-dione (3d).** Yellow crystals (from EtOAc), yield 86 %, mp 125-127 °C; IR mineral oil ($\nu_{max}$, $cm^{-1}$): 3120 w (NH), 1652 ($C^6$=O), 1619 ($C^2$=O in IHB). $^1$H NMR (400.1 MHz, DMSO-$d_6$): δH 1.27 (6H, s, $2CH_3$), 2.38 (3H, s, $C_6H_4CH_3$-p), 3.05 (2H, s, $C^4H_2$), 3.60 (3H, s, $OCH_3$), 3.71 (3H, s, $OCH_3$), 5.51 (1H, s, CH), 6.54 ($1H_{arom}$, s, CH), 6.73 ($1H_{arom}$, s, CH), 6.78-7.81 ($4H_{arom}$, m, 4CH), 10.63 (1H, s, NH, isoquinilin), 11.78 (1H, s, NH, pyridine). Anal. Calcd for $C_{25}H_{26}N_2O_4$ (418.19): C, 71.75; H, 6.26; N, 6.69%. Found: C, 71.64; H, 6.31; N, 6.12%.

**(*Z*)-3-(4a-methyl-1,3,4,4a,5,10b-hexahydrophenanthridin-6(2*H*)-ylidene)-4-phenylpyridine-2,6(1*H*,3*H*)-dione (3e).** Yellow crystals (from EtOAc), yield 85 %, mp 271-272 °C; IR mineral oil ($\nu_{max}$, $cm^{-1}$): 3100 (NHisoq, NHpyrid), 1649 ($C^6$=O), 1617 ($C^2$=O in IHB). $^1$H NMR (300.1 MHz, DMSO-$d_6$): δH 0.70 (3H, s, $C^{4a}CH_3$), 1.38-2.32 (8H, m, $(CH_2)_4$), 2.94, 2.98 (1H, dd, $C^{10b}H$, *J* 3.5 Hz), 5.59 (1H, s, CH), 6.82-7.27 ($9H_{arom}$, m, 9CH), 10.88 (1H, s, NH, isoquinoline), 12.08 (1H, s, NH, pyridine). Anal. Calcd for $C_{25}H_{24}N_2O_2$ (384.18): C, 78.10; H, 6.29; N, 7.29%. Found: C, 77.98; H, 6.49; N, 6.27%.

**X-ray diffraction study of the compound (3e).** X-Ray analysis of **3e** including data collection, cell refinement and data reduction was carried out with an Oxford Diffraction Xcalibur SCCD diffractometer using CrysAlisPro software package[10]. Analysis was accomplished on standard procedure (monochromatic MoKα-irradiation, ω-scanning with steps 1°, 295(5) K). Absorption correction was not applied (μ= 0.198 $mm^{-1}$). According to X-Ray data the crystal is triclinic, the space group P-1, a= 10.1661(12) Å, b= 11.4472(12) Å, c= 11.7668(9) Å, α= 117.488(10)°, β= 111.521(11)°, γ=90.013(9)°. θ range for data collection: 2.68 to 28.28°. 7167 Reflections were collected, independent reflections 5371 (Rint= 0.0182), 2740 reflections with I>2σ(I), completeness 97.8 %. The structure was solved by the direct method and refined by the full-matrix least-squares on $F^2$ method using SHELXTL program package[11]. Results of refinement: $R_1$= 0.0360, $wR_2$= 0. 0769 (for I>2σ(I)), $R_1$= 0.0828, $wR_2$= 0.0723 (for all data), S=1.000, largest diff. peak and hole 0.179 and -0.-164 ēÅ$^{-3}$.

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## Graphical Abstract