Chemistry of Heterocyclic Compounds, Vol. 42, No. 5, 2006

HETERO-DIELS–ALDER REACTION OF N-CYANOANILINE AND PYRIDINIUM CYANO-(ETHOXYCARBONYL)METHYLIDE WITH AROYLKETENES GENERATED *in situ* IN THERMOLYSIS OF 6-ARYL-2,2-DIMETHYL-1,3-DIOXIN-4-ONES

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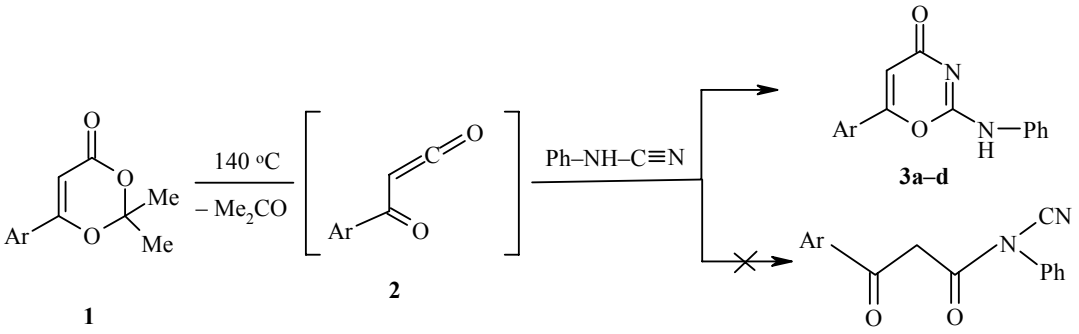
We have used thermolysis of 6-aryl-2,2-dimethyl-1,3-dioxin-4-ones in the presence of N-cyanoaniline, pyridinium cyano(ethoxycarbonyl)methylide, and 4-hydroxybenzonitrile to obtain the corresponding 6-aryl-2-phenylamino-1,3-oxazin-4-ones, pyridinium ethoxycarbonyl(4-oxo-6-aryl-4H-1,3-oxazin-2-yl)methylides, and p-cyanophenyl esters of 3-aryl-3-oxopropanoic acids. We present the results of a preliminary investigation of the biological activity of these compounds.

Keywords: 6-aryl-2,2-dimethyl-1,3-dioxin-4-ones, aroylketenes, 4-hydroxybenzonitrile, N-cyano-aniline, pyridinium cyano(ethoxycarbonyl)methylide, aroylacylation, biological activity, [4+2] cycloaddition.

6-Aryl-2,2-dimethyl-1,3-dioxin-4-ones (**1**) are convenient synthons for generation of arolylketenes **2** [1]. Aroylketenes readily aroylacylate aniline to form the corresponding anilides [2]. N-cyanoaniline (phenyl cyanamide) contains a cyano group in addition to an amino group, and when it is reacted with aroylketenes, the competing reaction of [4+2] cycloaddition at the cyano group is possible [3, 4].



3 a Ar = Ph, **b** Ar = 4-MeC_6H_4, **c** Ar = 4-$EtOC_6H_4$, **d** Ar = 4-ClC_6H_4

As has been established, the reaction of aroylketenes occurs exclusively at the cyano group to form 6-aryl-2-phenylamino-1,3-oxazin-4-ones **3a-d**.

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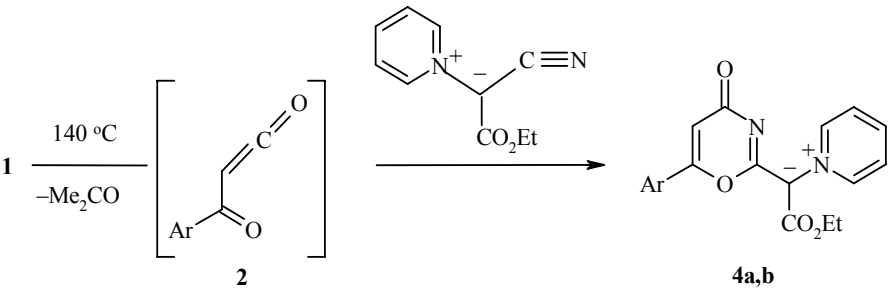
In the IR spectra of the synthesized compounds, there are signals from the carbonyl group in the 1650-1660 cm^{-1} region and signals from the NH group in the 3160-3300 cm-1 region. In the 1H NMR spectrum taken in DMSO-d_6, there are signals from aromatic protons of the two benzene rings in the 7.86-8.06 ppm region, and also a signal from the methine proton of the oxazine ring in the 6.46-6.60 ppm region and a broadened signal from the NH group in the 10.05-11.00 ppm range. The lack of characteristic absorption of the cyano group in the 2225-2245 cm^{-1} region is evidence in favor the structure of these compounds.

This reaction is classified as a hetero-Diels–Alder reaction, where the aroylketene acts as the diene and the C≡N bond of the reagent acts as the dienophile. According to the Sustman classification, it is classified as a diene synthesis reaction with an inverse electronic effect in the addends [5].

Upon thermolysis of dioxinones **1a,b** in the presence of pyridinium cyano(ethoxycarbonyl)methylide, the reaction also proceeds with participation of the C≡N bond to form pyridinium ethoxycarbonyl(4-oxo-6-aryl-4H-1,3-oxazin-2-yl)methylides **4a,b**.

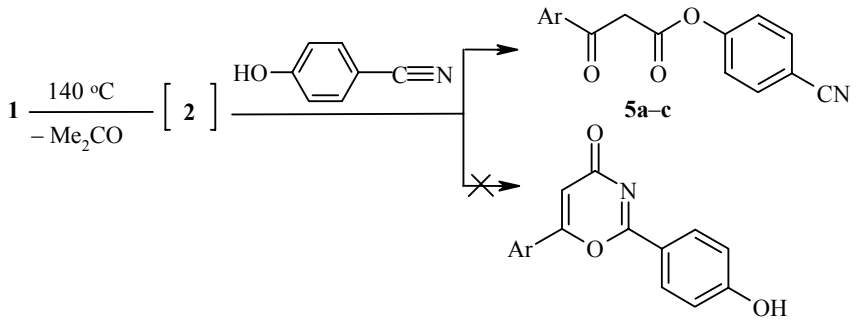


4 a Ar = Ph, **b** Ar = 4-MeC_6H_4

In the IR spectra of compounds **4a,b**, there is an intense band in the 1620-1670 cm^{-1} region due to superimposed vibrations of the carbonyls in ester and amide groups. In the ^{1}H NMR spectrum taken in $CDCl_3$, there are signals from the protons of the benzene and pyridine rings in the 7.00-8.60 ppm region, a singlet from the methine proton of the oxazine ring in the 6.48-6.50 ppm region, a triplet from the CH_3 group in the 0.88 ppm region, and a quadruplet from the CH_2 group of the ethoxycarbonyl substituent. The spectra obtained for compounds **4a,b** agree well with the spectra of structurally similar compounds [6, 7].

Replacing the ethoxycarbonyl group bonded to the ylide carbon atom by a benzoyl or arylamide group leads to tar formation in the reaction mixture, which is probably connected with the decreased electron-donor properties of the ylide carbon atom under the influence of these groups. This in turn passivates the cyano group and makes it impossible for that group to participate in the reaction as a dienophile.

When dioxinones **1** react with 4-hydroxybenzonitrile, the reaction of the aroylketenes occurs at the hydroxy group to form *p*-cyanophenyl esters of 3-aryl-3-oxopropanoic acids **5a-c**.



5 a Ar = Ph, **b** Ar = 4-MeC_6H_4, **c** Ar = 4-$EtOC_6H_4$

TABLE 1. Characteristics of Compounds **3-5**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
3a	$C_{16}H_{12}N_2O_2$	72.7 / 72.7	4.4 / 4.5	10.5 / 10.6	220-222	75
3b	$C_{17}H_{14}N_2O_2$	73.3 / 73.4	4.9 / 5.0	10.0 / 10.1	235-236	72
3c	$C_{18}H_{16}N_2O_3$	70.1 / 70.1	5.1 / 5.2	9.0 / 9.1	243-245	78
3d	$C_{16}H_{11}ClN_2O_2$*	64.3 / 64.3	3.6 / 3.7	9.3 / 9.4	250-252	84
4a	$C_{19}H_{16}N_2O_4$	67.7 / 67.9	4.9 / 4.8	8.1 / 8.3	224-225	65
4b	$C_{20}H_{17}N_2O_4$	68.7 / 68.8	4.8 / 4.9	7.9 / 8.0	231-232	68
5a	$C_{16}H_{11}NO_3$	72.4 / 72.5	4.0 / 4.1	5.1 / 5.3	106-108	40
5b	$C_{17}H_{13}NO_3$	73.0 / 73.1	4.3 / 4.6	4.8 / 5.0	115-116	45
5c	$C_{18}H_{15}NO_4$	69.7 / 69.9	4.8 / 4.8	4.3 / 4.5	132-134	38

* Found, %: Cl 11.7. Calculated, %: Cl 11.9.

It was previously established that the reaction of dioxinones **1** with 4-aminobenzonitrile proceeds analogously [8].

In the IR spectra of compounds **5a-c**, we observe intense absorption in the 1675-1690 cm^{-1} region, due to stretching vibrations of the ketone carbonyl, and also in the 1765-1770 cm^{-1} region, associated with stretching vibrations of the ester carbonyl. In the 2225-2245 cm^{-1} region, there is a signal from the C≡N bond. In the ^1H NMR spectra of these compounds taken in $CDCl_3$ solution, there is a singlet for two protons of the methylene group at 4.00-4.13 ppm and a group of signals from aromatic protons in the range 6.73-7.93 ppm. In addition to the signal from the protons of the methylene group, the spectrum contains weak signals from the methine proton at 5.66-5.80 ppm and from the proton of the enol hydroxyl at 11.97-12.05 ppm, which suggests that both the ketone and enol forms of compounds **5a-c** are present in the solutions. Judging from the integrated intensity of the signals for protons of the methylene and methine groups, the enol content is 10-30%. The IR and ^{1}NMR spectral data for esters **5a-c** agree well with the corresponding data for phenyl esters of aroylacetic acids in [9].

The synthesized compounds **3-5** were screened for analgesic activity by the "hotplate" method [10] and were screened for anti-inflammatory activity using the "carrageenin response" model [11]. Aminooxazinones **3a-c** had defensive reflex times of 25.9 sec, 19.2 sec, and 29.1 sec respectively, which is comparable with the activity of Voltaren (26 sec). For aminooxazinone **3d**, this parameter is 41 sec, i.e., it is 1.6 times better than the comparison standard. Compound **3a** inhibits edema by 5.5%; edema inhibition is 48.1% for **3b**, 31.6% for **3c**, and 23.3% for **3d**. That is, they have less anti-inflammatory activity than Voltaren, which displays 64.1% inhibition of edema. For oxazinones **4a,b**, the defensive reflex time is 21.3 sec and 23 sec and the inhibition of edema is 39% and 43% respectively. The indicated types of activity were not determined for esters **5a-c**. All the studied compounds showed moderate toxicity, with LD_{50} equal to 450-500 mg/kg or higher. The presence of analgesic activity in compounds **3** makes the search for analgesics in this series a promising approach [3].

EXPERIMENTAL

The IR spectra of compound **3-5** were taken on a UR-20 as nujol mulls. The ^{1}H NMR spectra were recorded on an RS-60 spectrometer (60 MHz), internal standard HMDS (δ 0.05 ppm). The homogeneity of the compounds was confirmed on Silufol-254 plates in the system 1:1 benzene–ether, visualization by iodine. The characteristics of the compounds are given in Table 1.

6-Aryl-2-phenylamino-1,3-oxazin-4-ones 3a-d. A mixture of dioxinone **1** (10 mmol) and N-cyanoaniline (10 mmol) was boiled for 20 min in xylene (15 ml). The solution was cooled down, and the precipitate was recrystallized from DMF.

Pyridinium Ethoxycarbonyl(4-oxo-6-aryl-4H-1,3-oxazin-2-yl)methylides 4a,b. Pyridinium cyano(ethoxycarbonyl)methylide (10 mmol) was added to a suspension of dioxinone **1** (10 mmol) in xylene (20 ml) and boiled for 20 min. The reaction mixture was cooled down, the precipitate was filtered out and recrystallized from DMF.

***p*-Cyanophenyl Esters of 3-Aryl-3-oxopropanoic Acids 5a-c.** A mixture of dioxinone **1** (10 mmol) and 4-hydroxybenzonitrile (10 mmol) was heated for 20 min in xylene (10 ml). The reaction mixture was cooled down, the precipitate was filtered out and recrystallized from xylene or CCl_4.

This work was done with the financial support of the Special Federal Program on Integration of Science and Higher Education in Russia (project No. IO573/1343).

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