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REACTION OF 6-ARYL-2,2-DIMETHYL-1,3-DIOXIN-4-ONES WITH CYANOAMINO COMPOUNDS

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Aroylketenes have been generated by thermolysis of 6-aryl-2,2-dimethyl-1,3-dioxin-4-ones. They take part in a 1,4-cycloaddition reaction at the C≡N bond of N-aryl or N,N-dialkyl-N-cyanoamines and of N'-phenyl-N-cyanoguanidine to form the corresponding 2-N-aryl-amino, 2-N,N-dialkylamino, and 2-N-phenylguanidino-6-aryl-1,3-oxazin-4-ones. p-Aminobenzonitrile and cyanoacetamide are acylated by aroylketenes to form the p-cyanophenylamide of p-toluylacetic acid and the cyano-acetamide of benzoylacetic acid.

Aroylketenes can be conveniently generated by the thermolysis of 5-aryl-2,3-dihydrofuran-2,3-diones [1] and they can then take part in 1,4-cycloadditions with aldehydes, ketones [2], azomethines [3], isocyanates [4], and other compounds containing multiple bonds [5]. The ability of compounds with the C≡N bond to take part in this reaction is restricted to those with a strongly activating electron donating group (N,N-dialkylcyanamines, cyanoic esters) [6]. Unsubstituted and monosubstituted cyanamides cannot take part in the cycloaddition reaction because their properties as BH nucleophiles cause opening of the 5-aryl-2,3-dihydrofuran-2,3-dione ring under conditions considerably milder than those demanded for generation of the aroylketene [7]. Aminonitriles containing unsubstituted or monosubstituted amino groups react in a similar manner [8].

In order to study the reaction of cyanoamino compounds with aroylketenes another method of generating the latter was used based on the thermolysis of 6-aryl-2,2-dimethyl-1,3-dioxin-4-ones (I). This occurs under significantly more severe conditions (140-145°C) than for the thermolysis of 5-aryl-2,3-dihydrofuran-2,3-diones (80-85°C). BH nucleophiles do not react with compounds I below the temperature for generating the aroylketenes [9]. (Formula, following page, below Table 1.)

Both mono and di-substituted cyanamides react with Ia-d to form 2-N-mono (II) and 2-N,N-disubstituted-6-aryl-1,3-oxazin-4-ones (III-VII). Unsubstituted cyanamide could not be used due to its very ready dimerization even with gentle heating.

The IR and PMR spectra of the compounds corresponded to those given in [6, 10-12].

Aroylketenes generated by thermolysis of Ia-e react at the C≡N bond of N'-phenyl-N-cyanoguanidine to form 2-N-phenylguanidino-6-aryl-1,3-oxazin-4-ones VIII-XI (Table 1).

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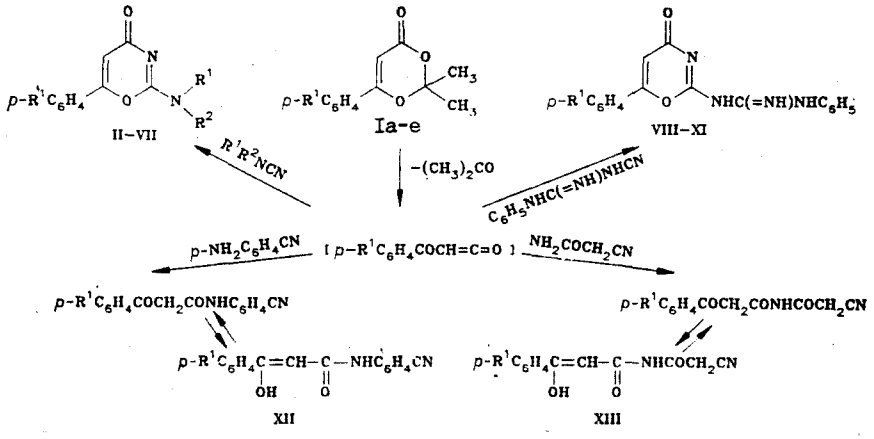
TABLE 1. Physicochemical Properties of II-XIII

Compound	R^1	R^2	R^3	Empirical formula	mp, °C	Yield, %
II	H	H	C_6H_4Cl-*o*	$C_{16}H_{11}ClN_2O_2$	201...202	82
III	CH_3	C_2H_5	C_2H_5	$C_{15}H_{18}N_2O_2$	90...91	77
IV	CH_3	C_2H_4CN	C_2H_4CN	$C_{17}H_{16}N_4O_2$	179...180	97
V	CH_3O	C_2H_4CN	C_2H_4CN	$C_{17}H_{16}N_4O_3$	220...221	93
VI	H	C_4H_9	C_4H_9	$C_{18}H_{24}N_2O_2$	90...91	40
VII	Cl	C_4H_9	C_4H_9	$C_{18}H_{23}ClN_2O_2$	134...135*	56
VIII	H	—	—	$C_{16}H_{14}N_4O_2$	231...232	98
IX	CH_3	—	—	$C_{17}H_{15}N_4O_2$	282...284	80
X	Br	—	—	$C_{16}H_{13}BrN_4O_2$	246...248	97
XI	Cl	—	—	$C_{16}H_{13}ClN_4O_2$	242...244	85
XII	CH_3	—	—	$C_{17}H_{14}N_2O_2$	173...174	82
XIII	H	—	—	$C_{12}H_{10}N_2O_3$	150...151†	90

*Lit. mp = 131.5-132.5°C [6].
†Lit. mp = 152-153°C [8].



I a R^1=H; b R^1=CH_3; c R^1=CH_3O; d R^1=Cl; e R^1=Br

The IR spectra of VIII-XI show an intense absorption for the oxazine carbonyl group at 1640-1665 cm^{-1} superimposed upon absorption for the exo- and endocyclic C=N bonds together with C_5–H absorption at 3070-3100 cm^{-1} and NH absorption near 3170-3175 and 3340-3370 cm^{-1}. The PMR spectra in DMSO-d_6 solvent show a singlet methine group signal at 6.33-6.48 ppm and a multiplet for the aromatic protons at 6.88-7.90 ppm. The NH group signals are obscured by those of the aromatic protons.

The mass spectrum of compound X shows a molecular ion peak with m/z 384/386. The presence of intense peaks with m/z 183/185 $[BrC_6H_4COCH{=}C{=}O]^+$ and 160 $[C_6H_5NHC(=NH)NHCN]^+$ unambiguously, confirms the structure. The IR, PMR, and mass spectra are in agreement with the corresponding data for 2-guanidino-6-methyl-1,3-oxazine-4-one [13].

Reaction of Ib with p-aminobenzonitrile gives the p-cyanophenylamide of p-toluylacetic acid (XII), the spectra of which are given in Table 2. Formation of this compound is evidently due to addition of the reagent amino group to the C=C bond of the cumulene system of the aroylketene which occurs more readily than the 1,4-cycloaddition to the C≡N bond. Compound Ia reacts similarly with cyanoacetamide to give the cyanoacetamide of benzoylacetic acid (XIII) which was identified with a known sample.

The PMR spectra of XII and XIII (Table 2) showed methylene, hydroxyl, and methine proton signals pointing to partial enolization for those compounds (10-20% enol form from integrated area ratios). Confirmation came from the positive reaction of the H-chelated ring with ferric chloride giving a cherry-violet coloration.

EXPERIMENTAL

IR spectra were recorded on a UR-20 instrument in vaseline mull and PMR spectra on an RS-60 (60 MHz) in DMSO-d_6. Mass spectra were measured on an MK-1320 instrument with an ionization energy of 70 eV and ionization chamber temperature of 260°C. Elemental analytical data (C, H, N, Halogen) for II-XIII agreed with that calculated.

TABLE 2. Spectral Characteristics of II-XIII

Compound	IR spectrum, cm^{-1}	PMR spectrum, ppm
II	1640, 3050, 3280	6,61 (1H, s, CH); 6,88...7,91 (9H arom., m.); 10,95 (1H, s, NH)
III	1632, 3070	1,25 (6H, t, $2CH_3$); 2,31 (3H, s, CH_3); 3,55 (4H, s, $2CH_2$); 6,35 (1H, s, CH); 6,98...7,71 (4H, q, C_6H_4)
IV	1655, 2275, 3080	2,29 (3H, s, CH_3); 2,89 (2H, t, CH_2); 3,83 (2H, t, CH_2); 6,45 (1H, s, CH); 7,06...8,00 (4H, m, C_6H_4)
V	1645, 2267, 3080	2,55 (3H, s, CH_3O); 3,00 (2H, t, CH_2); 3,80 (2H, t, CH_2); 6,37 (1H, s, CH); 6,78...7,78 (4H, q, C_6H_4)
VI	1665, 3070	0,71...3,71 (18H, m, $2C_4H_9$); 6,25 (1H, s, CH); 7,11...7,81 (5H, m., C_6H_5)
VII	1660, 3070	0,41...3,68 (18H, m, $2C_4H_9$); 6,31 (1H, s, CH); 7,05...7,51 (4H, m, C_6H_4)
VIII	1650, 3090, 3170, 3360	6,43 (1H, s, CH); 6,88...7,81 (12H, m, $2C_6H_5$, 2NH)
IX	1660, 3085, 3175, 3340	2,33 (3H, s, CH_3); 6,33 (1H, s, CH); 7,05...7,71 (11H, m, C_6H_4, C_6H_5, 2NH)
X	1665, 3100, 3170, 3370	6,48 (1H, s, CH); 6,95 (11H, m, C_6H_5, C_6H_4, 2NH)
XI	1665, 3090, 3175, 3350	6,48 (1H, s, CH); 7,05...7,81 (11H, m, C_6H_5, C_6H_4, 2NH)
XII	1640...1675, 2255, 3240	2,23 (3H, s, CH_3); 3,45 (2H, s CH_2); 5,83 (1H, s, CH); 7,05...8,05 (8H, m, $2C_6H_4$); 10,45 (1H, s, H); 13,41 (1H, s, OH)
XIII	1695, 2260, 3150...3250	3,93 (2H, s, CH_2); 4,25 (2H, s CH_2); 6,34 (1H, s, CH); 7,21...7,95 (5H, s, C_6H_5); 12,82 (1H, s, OH)

2-N-Mono Substituted and 2-N,N-Disubstituted-6-aryl-1,3-oxazin-4-ones (II-VII). A mixture of I (0.01 mole) and N,N-dialkyl or N-aryl-N-cyanoamine (0.01 mole) were heated for 20 min at 140°C. The product was recrystallized from toluene.

2-N-Phenylguanidino-6-aryl-1,3-oxazin-4-ones (VIII-XI). Compound I (0.01 mole) and N'-phenyl-N-cyanoguanidine (0.01 mole) were heated for 15 min in mesitylene (10 ml), cooled, and the product recrystallized from acetic acid.

p-Cyanophenylamide of p-Toluylacetic Acid (XII). Compound I (0.01 mole) and p-aminobenzonitrile (0.01 mole) were heated for 15 min at 140°C, cooled, and the product recrystallized from dioxane.

Cyanoacetamide of Benzoylacetic Acid (XIII). Compound I (0.01 mole) and cyanoacetamide (0.01 mole) were heated for 10 min at 140°C. The product was recrystallized from ethanol.

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