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Studies on Heterocyclic Compounds. X.[1] Dealkoxycarbonylation of Ethyl 2-Arylamino-4-oxo-4,5-dihydrofuran-3-carboxylates

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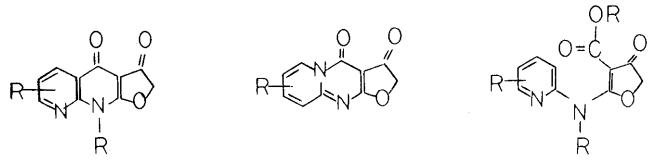
The derivatives of ethyl 2-arylamino-4-oxo-4,5-dihydrofuran-3-carboxylates (1) undergo dealkoxycarbonylation when they are refluxed in dimethylformamide. A mechanism is proposed.

Keywords dealkoxycarbonylation; thermal cyclization; dimethylformamide; 2-arylamino-4-oxo-4,5-dihydrofuran; nucleophile

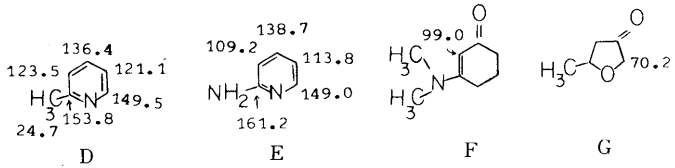
In a previous paper[1] of this series, we reported the syntheses and antiallergic activities of tetrahydrofuro[2,3-*b*]naphthyridine-3,4-diones (A) and dihydropyrido[1,2-*a*]-furo[2,3-*d*]pyridine-3,4-diones (B). Most of these two types of compounds showed significant activities.[1] In order to obtain more active compounds, other analogs were synthesized. However, the yield of one of the synthetic processes involving thermal cyclization of ethyl 2-pyridylamino-4-oxo-4,5-dihydrofuran-3-carboxylates (C) to A or B was



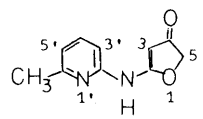
A B C

poor (71—78%). To improve the yield, various reaction conditions were tested. When dimethylformamide (DMF) was used in place of diphenylether as the cyclization medium, an interesting product resulted. In this paper, we will discuss this novel dealkoxycarbonylation of ethyl 2-arylamino-4-oxo-4,5-dihydrofuran-3-carboxylates (**1a—d**).

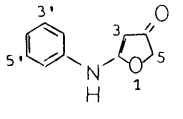
According to a modification of the previous report,[1] ethyl 2-(6′-methyl-2′-pyridyl)amino-4-oxo-4,5-dihydrofuran-3-carboxylate (**1a**) was dissolved in anhydrous DMF in place of diphenylether and refluxed for 6 h. Column chromatography gave **2a** (mp 208—210 °C, 55%). The molecular formula of compound **2a** had been established by high-resolution mass spectroscopy as $C_{10}H_{10}N_2O_2$. Other spectral data were: IR (KBr) cm^{-1}: 1668 (C=O); ^{1}H-NMR (CF_3COOD) δ ppm: 2.88 (3H, s, 6′-CH_3), 5.45 (2H, s, -O-CH_2-CO), 6.00 (1H, s, $H_{6'}$) and 7.52—8.60 (3H, m, $H_{3'}$-$H_{5'}$). From the above data, compound **2a** can be assigned as 2-(6′-methyl-2′-pyridyl)amino-4-oxo-4,5-dihydrofuran. ^{13}C-NMR spectra of compound **2a** were also examined and the assignments were made by analogy with model compounds D, E, F, G[2] and **1a**.



D E F G



2a



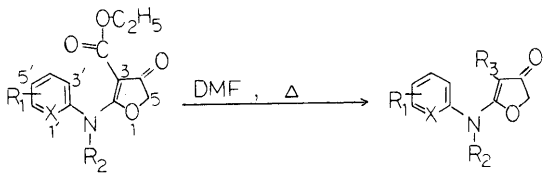
2d

When ethyl 2-(2′-pyridyl)amino-4-oxo-4,5-dihydrofuran-3-carboxylate (**1b**) and ethyl 2-(4′-methyl-2′-pyridyl)amino-4-oxo-4,5-dihydrofuran-3-carboxylate (**1c**) were refluxed in DMF, 2-(2′-pyridyl)amino-4-oxo-4,5-dihydrofuran (**2b**) and 2-(4′-methyl-2′-pyridyl)amino-4-oxo-4,5-dihydrofuran (**2c**) were formed, respectively.

We were interested in this facile dealkoxycarbonylation and the reaction mechanism was thus investigated. In order to determine whether the presence of the pyridine ring is necessary, ethyl 2-anilino-4-oxo-4,5-dihydrofuran-3-carboxylate (**1d**) was used as a starting material in the same procedure. As expected, the dealkoxycarbonylation product, 2-anilino-4-oxo-4,5-dihydrofuran (**2d**), was obtained. Therefore, the nitrogen atom of the pyridine ring is not involved in the dealkoxycarbonylation.

The mechanism of the dealkoxycarbonylation of **1a—d** is proposed to be as shown in Chart 2. In DMF, **1a—d** might tautomerize into H, and then the nitrogen of DMF nucleophilically attacks the carbonyl group of the ester moiety to conduct the dealkoxycarbonylation reaction. In order to obtain support for his proposed mechanism, two other experiments were carried out. When using an *N*-substituted compound, ethyl *N*-methyl-2-(6′-methyl-2′-pyridyl)amino-4-oxo-4,5-dihydrofuran-3-carboxylate (**1e**), as a starting material, no reaction occurred after the same procedure as previously mentioned, indicating that the presence of the tautomer H is necessary. When the cyclized compound A was used as a starting material no reaction occurred, indicating that the dealkoxycarbonylation does not occur after cyclization.

The mechanism shown in Chart 2 corresponds with that of dealkoxycarbonylation of α-ketoesters and related compounds proposed by Krapcho.[3,4] Nucleophiles such as



1 2

	X	R_1	R_2	R_3
1a:	N	6′-CH_3	H	
1b:	N	H	H	
1c:	N	4′-CH_3	H	
1d:	CH	H	H	
1e:	N	6′-CH_3	CH_3	
2a:	N	6′-CH_3	H	H
2b:	N	H	H	H
2c:	N	4′-CH_3	H	H
2d:	CH	H	H	H
2e:	N	6′-CH_3	CH_3	$COOC_2H_5$

Chart 1

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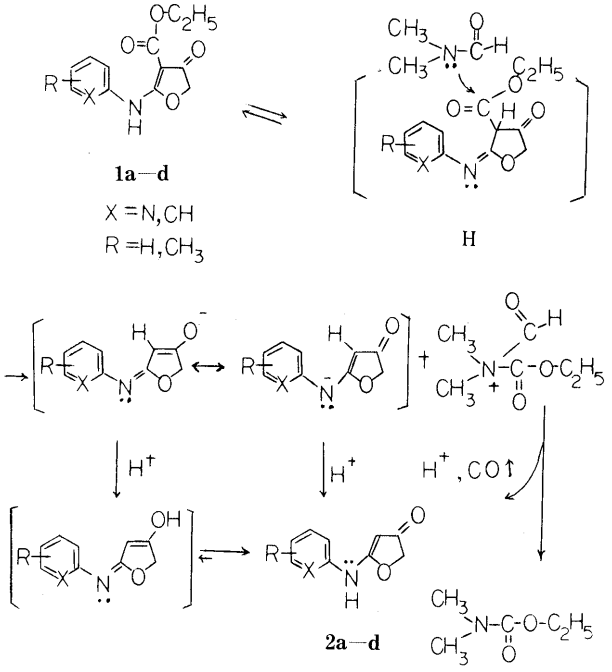

Chart 2

CN^-, Cl^-, ... H_2O were involved in the latter, whereas our mechanism used a milder nucleophile (nitrogen of DMF).

In summary, the derivatives of ethyl 2-arylamino-4-oxo-4,5-dihydrofuran-3-carboxylate (**1**) are prone to undergo dealkoxycarbonylation when heated in DMF. Therefore, compounds having such a structure should not be allowed to come into contact with DMF when thermal cyclization is desired.

Experimental

All melting points are uncorrected. Infrared (IR) spectra were recorded on a Shimadzu IR-400 spectrometer in KBr. Nuclear magnetic resonance (NMR) spectra were taken at 90 MHz, on a JEOL FX-90Q spectrometer with tetramethylsilane (TMS) as an internal reference in $CDCl_3$, CF_3COOD or dimethyl sulfoxide-d_6 (DMSO-d_6). The following abbreviations are used s = singlet, d = doublet and m = multiple. Mass spectra (MS) were measured with an HP 5995 GC-MS instrument and a JEOL JMS-D300 spectrometer.

2-(6′-Methyl-2′-pyridyl)amino-4-oxo-4,5-dihydrofuran (2a) Ethyl 2-(6′-methyl-2′-pyridyl)amino-4-oxo-4,5-dihydrofuran-3-carboxylate (1 g, 3.8 mmol) was suspended in dry DMF (50 ml) and heated to reflux for 6 h. The solvent was removed by vacuum evaporation and the residue was purified by chromatography on a silica gel (80 g) column. Elution with $CHCl_3$–EtOH (97 : 3) gave **2a** as a light green solid (0.38 g, 55%). mp 208—210 °C (from ethanol). IR (KBr) cm^{-1}: 3170 (NH), 1688 (C=O). ^{13}C-NMR (CF_3COOD) δ ppm: 23.76 (6′-CH_3), 72.46 (C_5), 85.38 (C_3), 109.67 ($C_{3'}$), 117.56 (C_5), 138.45 ($C_{4'}$), 150.40 ($C_{6'}$), 156.60 ($C_{2'}$), 175.99 (C_2), 196.88 (C_4). High-resolution MS *m/z*: M^+ Calcd for $C_{10}H_{10}N_2O_2$: 190.0743. Found: 190.0740.

2-(2′-Pyridyl)amino-4-oxo-4,5-dihydrofuran (2b) Ethyl 2-(2′-pyridyl)-amino-4-oxo-4,5-dihydrofuran-3-carboxylate (1 g, 4.0 mmol) was refluxed in dry DMF (50 ml) in the same manner as described for **2a** to afford **2b** (0.38 g, 55%) as a colorless solid. mp 238—240 °C (from ethanol). IR (KBr) cm^{-1}: 3170 (NH), 1625 (C=O). ^{1}H-NMR (CF_3COOD) δ ppm: 5.44 (2H, s, –OCH_2–CO–), 5.94 (1H, s, H_3), 7.67—8.74 (4H, m, $H_{3'}$–$H_{6'}$). High-resolution MS *m/z*: M^+ Calcd for $C_6H_8N_2O_2$: 176.0586. Found: 176.0588.

2-(4′-Methyl-2′-pyridyl)amino-4-oxo-4,5-dihydrofuran (2c) Ethyl 2-(4′-methyl-2′-pyridyl)amino-4-oxo-4,5-dihydrofuran-3-carboxylate (1 g, 3.8 mmol) was refluxed in dry DMF (50 ml) in the same manner as described for **2a** to afford **2c** (0.41 g, 57%) as a colorless solid. mp 242—245 °C (from ethanol). IR (KBr) cm^{-1}: 3180 (NH), 1625 (C=O). ^{1}H-NMR (DMSO-d_6) δ ppm: 2.35 (3H, s, 4′-CH_3), 4.50 (2H, s, –OCH_2–CO–), 5.70 (1H, s, H_3), 7.61 (1H, d, J=6 Hz, $H_{5'}$), 7.88 (1H, s, $H_{3'}$), 8.40 (1H, d, J=6 Hz, $H_{6'}$). High-resolution MS *m/z*: M^+ Calcd for $C_{10}H_{10}N_2O_2$: 190.0743. Found: 190.0753.

2-Anilino-4-oxo-4,5-dihydrofuran (2d) Ethyl 2-anilino-4-oxo-4,5-dihydrofuran-3-carboxylate (1 g, 4.5 mmol) was refluxed in dry DMF (50 ml) in the same manner as described for **2a** to afford **2d** (0.43 g, 55%) as a colorless solid. mp 201—203 °C. IR (KBr) cm^{-1}: 3180 (NH), 1650 (C=O). ^{1}H-NMR (DMSO-d_6) δ ppm: 4.52 (2H, s, –OCH_2–CO–), 4.80 (1H, s, H_3), 7.00—7.50 (5H, m, $H_{2'}$–$H_{6'}$). High-resolution MS *m/z*: M^+ Calcd for $C_{10}H_9NO_2$: 175.0634. Found: 175.0640.

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