New Synthesis of 2(1*H*)-Pyridone Derivatives

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The reaction of N^1-acyl-2-ethoxycarbonylacetamidrazones **1** with diethyl ethoxymethylenemalonate (EMME) is reported. By refluxing equimolecular amounts of **1** and EMME in DMSO/toluene (or ethanol) solution, the 1-acylamino-2(1*H*)-pyridones **2** were obtained in good yield. When the reaction was performed in ethanolic solution in the presence of triethylamine, the 6-acylhydrazino-2(1*H*)-pyridones **3** were obtained.

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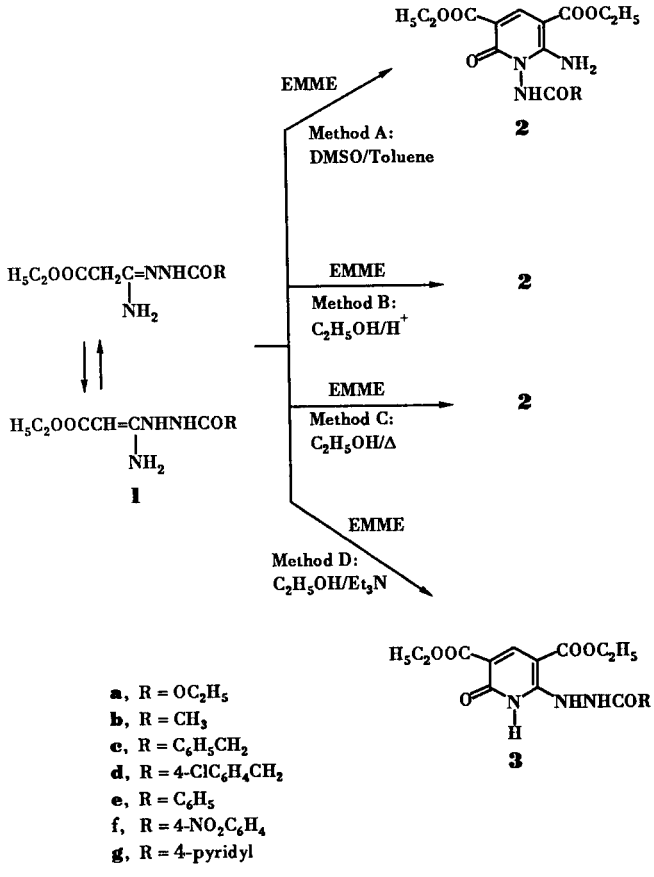
Because of their interesting biological properties, 2-amino- or 2-hydroxy-3-pyridinecarboxylic acid derivatives have been studied rather extensively in recent years [1]. In a previous study we reported a convenient method for the synthesis of 6-amino and 6-alkyloxy-2(1*H*)-pyridone derivatives by reacting ethyl cyanoacetimidate, ethyl ethoxycarbonylacetimidate and related acetamidines with diethyl ethoxymethylenemalonate (EMME) under very mild conditions [2]. In the present study we report on the reaction between N^1-acylacetamidrazones **1** and EMME; the reaction medium and conditions determine the class of compounds obtained (Scheme 1).

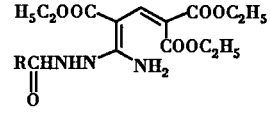
Scheme 1



The condensation of equimolecular amounts of **1** and EMME, under reflux in dimethyl sulphoxide/toluene 1:1 (v/v) gives the diethyl 1-acylamino-6-amino-1,2-dihydro-2-oxo-3,5-pyridinedicarboxylates **2** in only one stage. By heating under reflux in ethanol in the presence or in the absence of acetic acid the same compounds **2** were obtained. The reaction between **1a-c,e** and EMME in ethanol and triethylamine gave compounds **3**. When possible, due to the low solubility of the acetamidrazones **1**, the reaction was carried out in ethanol at room temperature. From the reaction between **1b** and EMME a mixture of pyridones **2b** and **3b** was obtained in a 3:1 ratio. The results of the analytical data of compounds **2** and **3** and those of the reaction conditions are reported in Tables 1,2 and 3 respectively.

More probably the type of pyridone obtained is related to the intermediate dienamine **A** or **B** of the reaction, which we have not been able to isolate.

A

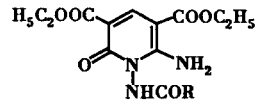


B

Both isomers were formed in ethanol at room temperature and gave the pyridones **2** and **3** after intramolecular cyclization. From the products obtained under the different reaction conditions, it can be hypothesized that the type and quantity of pyridone isomers formed are related to the thermodynamic stability of the two intermediate diastereoisomers **A** and **B**. In a different approach the pyridones **3** have been synthesized from the diethyl 6-ethoxy-1,2-dihydro-2-oxo-3,5-pyridinedicarboxylate (**4**) previously described [2]. The ethoxy group of compound **4** was converted into a hydrazino group by treatment with hydrazine hydrate in ethanol to yield compound **5** which was subsequently acylated into the corresponding compounds **3** (Scheme 2). The physical and spectral data of compounds **3b**, **3c** and **3e** thus obtained agree with those of the compounds obtained with method D.

Table 1

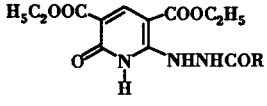
Physical and Analytical Data of Compounds **2**



Compound No.	R	Mp (°C)	Crystallization solvent	Formula	Analysis % Calcd. C	H	N	Found C	H	N
2a	C_2H_5O	193-194	Benzene	$C_{14}H_{19}N_3O_7$	49.26	5.61	12.31	49.29	5.63	12.36
2b	CH_3	234-235	2-Ethoxyethanol	$C_{13}H_{17}N_3O_6$	50.16	5.50	13.50	50.20	5.47	13.45
2c	$C_6H_5CH_2$	224-225	2-Ethoxyethanol	$C_{19}H_{21}N_3O_6$	58.91	5.45	10.85	58.86	5.42	10.89
2d	4-$ClC_6H_4CH_2$	251-252	2-Ethoxyethanol	$C_{19}H_{20}ClN_3O_6$	54.09	4.78	9.96	54.15	4.75	9.98
2e	C_6H_5	225-226	Acetonitrile	$C_{18}H_{19}N_3O_6$	57.90	5.13	11.26	57.83	5.10	11.22
2f	4-$NO_2C_6H_4$	229-230	Acetonitrile	$C_{18}H_{18}N_4O_8$	51.67	4.34	13.39	51.63	4.33	13.43
2g	4-pyridyl	229-230	Ethanol	$C_{17}H_{18}N_4O_6$	54.54	4.85	14.97	54.60	4.86	14.94

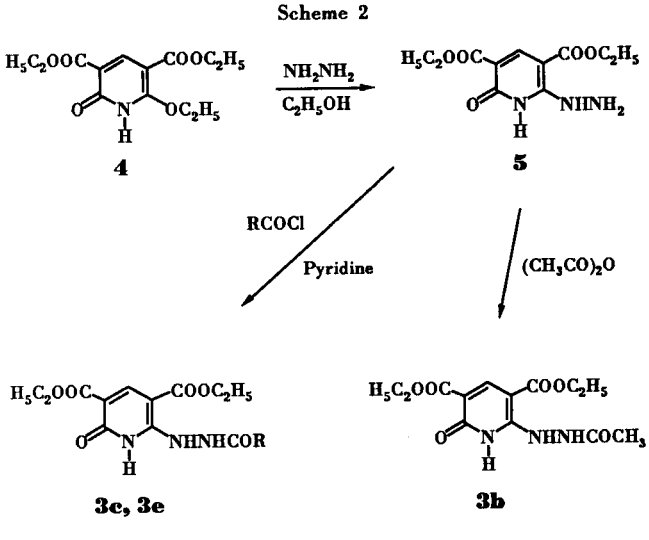
Table 2

Physical and Analytical Data of Compounds **3**



Compound No.	R	Mp (°C)	Crystallization solvent	Formula	Analysis % Calcd. C	H	N	Found C	H	N
3a	C_2H_5O	193-194	Acetone	$C_{14}H_{19}N_3O_7$	49.26	5.61	12.31	49.20	5.64	12.35
3b	CH_3	270-271	2-Ethoxyethanol	$C_{13}H_{17}N_3O_6$	50.16	5.50	13.50	50.20	5.47	13.46
3c	$C_6H_5CH_2$	199-200	1-Propanol	$C_{19}H_{21}N_3O_6$	58.91	5.45	10.85	58.87	5.44	10.88
3e	C_6H_5	279-280	2-Ethoxyethanol	$C_{18}H_{19}N_3O_6 \cdot H_2O$	55.24	5.41	10.74	55.30	5.38	10.70

Scheme 2



The structures of pyridones **2** and **3** agree with the ir and ^1H nmr spectroscopic data reported in Table 4. In the ^1H nmr spectra of pyridones **2**, in addition to the H-4 signal at δ 8.50-8.57, there are the downfield resonances of the NH_2 and NHCO groups that disappear after treatment with deuterium oxide. The protons of the primary amine group in pyridones **2**, except for **2a** and **2g**, give rise to two distinct singlets. The signal relating to the NH amide is shifted downfield (δ 9.84-11.36). The ^1H nmr spectra of the pyridones **3** show the H-4 chemical shift at δ 8.43-8.45, and that of the pyridine ring proton H-1 at δ 11.54-11.68. The protons of the NHNHCOR group resonate at fields in the range δ 9.35-10.10. In the ir spectra the absorption of NHNHCO is characterised by the presence of one single band between 3260 and 3240, while several absorption bands are present in the pyridones **2** in the region between 3480-3100.

Table 3

Yield % of Compounds **2** and **3**

Compound No.	Reaction Methods (hours) A	B	C	D
2a	50 (0.5)	20 (3)	30 (1)	
2b	67 (0.5)	32 (1)	87 (4)	
2c	65 (0.5)	26 (2)	20 (24)	
2d	71 (0.5)	25 (6)	16 (12)	
2e	85 (0.5)	25 (4)	45 (12)	
2f	67 (0.5)	30 (4)	34 (12)	
2g	50 (0.5)	16 (12)	20 (24)	
3a				20 (24)
3b				50 (24)
3c				35 (24)
3e				27 (96)

A: DMSO/Toluene 1:1, B: Ethanol, C: Ethanol/Acetic Ac., D: Ethanol/Et_3N.

EXPERIMENTAL

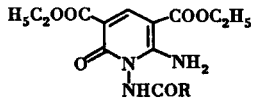
Melting points were determined on Köfler hot stage and are uncorrected. The ir spectra were obtained in Nujol with a Perkin-Elmer 398 spectrophotometer. The ^1H nmr spectra were recorded for hexadeuteriodimethyl sulphoxide solution with a Varian Unity 300 spectrometer; chemical shifts are reported in ppm from tetramethylsilane as an internal standard and are given in δ units. The elemental analyses (C,H,N) were carried out with a Carlo Erba model 1106 Elemental Analyzer. The N^1-acyl-2-ethoxycarbonylacetamidrazones **1a-e** were obtained by a previously described procedure [3].

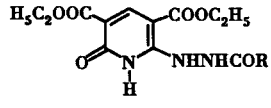
N^1-(4-Nitrobenzoyl)-2-ethoxycarbonylacetamidrazone (**1f**).

A mixture of ethyl 3-ethoxy-3-iminopropionate (10 mmoles) and 4-nitrobenzoylhydrazine (10 mmoles) in 100 ml of anhydrous ethanol was heated at 70-75° for 5 minutes and stirred at room temperature for 4 hours. The precipitate formed was collected by filtration and thoroughly washed with ethyl ether, mp 187-188° (from 1-propanol), yield 87%; ir (Nujol): 3280, 3100, 1745, 1680

Table 4

Spectroscopic Data of Compounds **2** and **3**





Compound No.	IR ν cm^{-1}	^{1}H-NMR δ (ppm), J (Hz)
2a	3400, 3280, 1780, 1740, 1690	1.16-1.26 (m, 9H, $3CH_3$), 4.07-4.24 (m, 6H. $3CH_2$), 8.50 (s, 1H, H-4), 8.69 (s, 2H, NH_2), 9.84 (s, 1H, NHCO)
2b	3280, 3100, 1710, 1695, 1670	1.18 (t, 3H, CH_3, J = 7.1), 1.24 (t, 3H, CH_3, J = 7.1), 2.01 (s, 3H, CH_3), 4.11 (q, 2H, CH_2, J = 7.1), 4.21 (q, 2H, CH_2, J = 7.1), 8.50 (s, 1H, H-4), 8.55, 8.68 (s, 2H, NH_2), 10.44 (s, 1H, NHCO)
2c	3350, 3290, 3240, 3190, 1740, 1680, 1650	1.17 (t, 3H, CH_3, J = 6.8), 1.24 (t, 3H, CH_3, J = 7.3), 3.68 (AB system, 2H, CH_2, J = 15.7), 4.11 (q, 2H, CH_2, J = 6.8), 4.21 (q, 2H, CH_2, J = 7.3), 7.29 (m, 5H, Ar), 8.50 (s, 1H, H-4), 8.62, 8.73 (s, 2H, NH_2), 10.70 (s, 1H, NHCO)
2d	3340, 3290, 3240, 3190, 1740, 1680, 1650	1.18 (t, 3H, CH_3, J = 7.1), 1.24 (t, 3H, CH_3, J = 7.1), 3.69 (AB system, 2H, CH_2, J = 15.7), 4.11 (q, 2H, CH_2, J = 7.1), 4.21 (q, 2H, CH_2, J = 7.1), 7.34 (m, 4H, Ar), 8.50 (s, 1H, H-4), 8.62, 8.73 (s, 2H, NH_2), 10.70 (s, 1H, NHCO)
2e	3380, 3260, 1730, 1680, 1660	1.18 (t, 3H, CH_3, J = 7.1), 1.26 (t, 3H, CH_3, J = 7.1), 4.12 (q, 2H, CH_2, J = 7.1), 4.23 (q, 2H, CH_2, J = 7.1), 7.52, 7.62, 7.97 (m, 5H, Ar), 8.56 (s, 1H, H-4), 8.74, 8.76 (s, 2H, NH_2), 10.98 (s, 1H, NHCO)
2f	3480, 3340, 3240, 1735, 1675	1.17 (t, 3H, CH_3, J = 7.1), 1.26 (t, 3H, CH_3, J = 7.1), 4.12 (q, 2H, CH_2, J = 7.1), 4.23 (q, 2H, CH_2, J = 7.1), 8.18, 8.38 (d, 4H, Ar), 8.57 (s, 1H, H-4), 8.80, 8.87 (s, 2H, NH_2), 11.36 (s, 1H, NHCO)
2g	3370, 3230, 1740, 1690, 1660	1.17 (t, 3H, CH_3, J = 7.1), 1.26 (t, 3H, CH_3, J = 7.1), 4.12 (q, 2H, CH_2, J = 7.1), 4.23 (q, 2H, CH_2, J = 7.1), 7.86, 8.80 (d, 4H, Py), 8.57 (s, 1H, H-4), 8.84 (s, 2H, NH_2), 11.33 (s, 1H, NHCO)
3a	3240, 1725, 1685, 1630	1.13-1.26 (m, 9H, $3CH_3$), 4.02-4.23 (m, 6H, $3CH_2$), 8.46 (s, 1H, H-4), 9.30 (s, 1H, NHNHCO), 10.01 (s, 1H, NHNHCO), 11.51 (s, 1H, H-1)
3b	3260, 1730, 1690, 1630	1.17-1.26 (m, 6H, $2CH_3$), 1.87 (s, 3H, CH_3), 4.09-4.24 (m, 4H, $2CH_2$), 8.45 (s, 1H, H-4), 9.97 (s, 2H, NHNHCO), 11.54 (s, 1H, H-1)
3c	3250, 1730, 1700, 1630	1.19 (t, 3H, CH_3, J = 6.8), 1.23 (t, 3H, CH_3, J = 6.8), 3.53 (s, 2H, CH_2), 4.14 (q, 2H, CH_2, J = 6.8), 4.20 (q, 2H, CH_2, J = 6.8), 7.25 (m, 5H, Ar), 8.45 (s, 1H, H-4), 10.02 (s, 1H, NHNHCO), 10.10 (s, 1H, NHNHCO), 11.60 (s, 1H, H-1)
3e	3540, 3280, 1715, 1670, 1615	1.19 (t, 3H, CH_3, J = 7.1), 1.26 (t, 3H, CH_3, J = 6.8), 4.10 (q, 2H, CH_2, J = 6.8), 4.19 (q, 2H, CH_2, J = 7.1), 7.30, 7.94 (m, 5H, Ar), 8.43 (s, 1H, H-4), 9.35 (br s, 2H, NHNHCO), 11.68 (s, 1H, H-1)

cm^{-1}; ^1H nmr (hexadeuteriodimethyl sulphoxide): δ 1.13 (t, 3H, CH_3), 3.60 (s, 2H, CH_2), 4.10 (q, 2H, CH_2), 7.75 (br s, 2H, NH_2), 8.17 (m, 4H, Ar).

Anal. Calcd. for $C_{12}H_{14}N_4O_5$: C, 48.98; H, 4.80; N, 19.04. Found: C, 48.90; H, 4.82; N, 19.00.

N^1-Isonicotinoyl-2-ethoxycarbonylacetamidrazone (**1g**).

This compound was obtained from ethyl 3-ethoxy-3-iminopropionate and isonicotinoylhydrazine in the same way for **1f**, mp 184-185° (from 1-propanol), yield 90%; ir (Nujol): 3360, 3050, 1730, 1675 cm^{-1}; ^1H nmr (hexadeuteriodimethyl sulphoxide): δ 1.12 (t, 3H, CH_3), 3.60 (s, 2H, CH_2), 4.18 (q, 2H, CH_2), 7.35 (br s, 2H, NH_2), 7.84 (d, 2H, Ar), 8.60 (d, 2H, Ar).

Anal. Calcd. for $C_{11}H_{14}N_4O_3$: C, 52.79; H, 5.64; N, 22.39. Found: C, 52.71; H, 5.63; N, 22.35.

Diethyl 1-Acylamino-6-amino-1,2-dihydro-2-oxo-3,5-pyridinedicarboxylates **2**.

Method A. Reaction in Dimethyl Sulphoxide/Toluene.

A solution of **1** (5 mmoles) and EMME (5 mmoles) in dimethyl sulphoxide/toluene 1:1 (v/v) (5 ml) was refluxed for 30 minutes. The toluene was evaporated at reduced pressure and 50 ml of water was added. The solid was collected by filtration and was crystallized to give the compounds **2** in 50-85% yields.

Method B. Reaction in Ethanol.

A solution of **1** (10 mmoles) and EMME (10 mmoles) in 50 ml of anhydrous ethanol was refluxed for the time reported in Table 3. After removal of the solvent, the residue was collected and crystallized to give **2** in 16-32% yields. Since acetamidrazone **1b** is the most soluble of compounds **1** it was possible to react **1b** (10 mmoles) with EMME (10 mmoles) in 50 ml of anhydrous ethanol at room temperature. After 24 hours the solvent was evaporated at reduced pressure. The residue was washed with water and tritured with ethyl acetate to give a solid that was filtered off (0.5 g) and identified as a mixture of **2b** (75%) and **3b** (25%). The isomeric composition of the mixture was evaluted by integrating the area of the H-4 signal.

Method C. Reaction in Presence of Acetic Acid.

Acetic acid (1 ml) was added to a solution of **1** (10 mmoles) and EMME (10 mmoles) in 50 ml of ethanol. The resulting solution was refluxed for the time reported in Table 3. After removal of the solvent, the residue was poured in water (50 ml) and neutralized. The resulting solid was crystallized and identified as compound **2**.

Diethyl 6-Acylhydrazino-1,2-dihydro-2-oxo-3,5-pyridinedicarboxylates **3**.

Method D. Reaction in Triethylamine.

A solution of **1** (10 mmoles), EMME (10 mmoles) and triethylamine (1 ml) in ethanol (50 ml) was stirred at room temperature for the time reported in Table 3. After removal of the solvent, the syrupy residue was treated with ethyl acetate, filtered, crystallized and identified as compound **3**.

Diethyl 6-Hydrazino-1,2-dihydro-2-oxo-3,5-pyridinedicarboxylate (**5**).

Hydrazine hydrate (10 mmoles) was added to a solution of **4** (5 mmoles) in ethanol (20 ml) and the solution was refluxed for 2 hours. The formed precipitate was filtered and recrystallized from ethanol, mp 210-211°, yield 70%; ir (Nujol): 3300, 3260, 3220, 1720, 1680, 1640 cm^{-1}; ^1H nmr (hexadeuteriodimethyl sulphoxide): δ 1.18 (t, 3H, CH_3), 1.22 (t, 3H, CH_3), 4.10 (q, 2H, CH_2), 4.17 (q, 2H, CH_2), 6.20 (br s, 3H, $NHNH_2$), 8.42 (s, 1H, H-4), 9.65 (s, 1H, H-1).

Anal. Calcd. for $C_{11}H_{15}N_3O_5$: C, 49.07; H, 5.62; N, 15.61. Found: C, 49.05; H, 5.60; N, 15.64.

Diethyl 6-Acetylhydrazino-1,2-dihydro-2-oxo-3,5-pyridinedicarboxylate (**3b**).

Compound **5** (2 mmoles) in acetic anhydride (3 ml) was stirred at room temperature for 10 minutes. The formed solid was collected by filtration washed with ethyl ether and recrystallized from 2-ethoxyethanol to give compound **3b** in 73% yield.

Diethyl 6-Acylhydrazino-1,2-dihydro-2-oxo-3,5-pyridinedicarboxylate **3c,e**.

Acylchloride (2 mmoles) was added to an ice-cooled solution of **5** (2 mmoles) in dry pyridine (1 ml). The solution was stirred at 0° for 3 hours. The obtained precipitate was washed with water and recrystallized from the appropriate solvent to give **3c** and **3e** in 65% and 95% yield respectively.

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