Chemistry of Heterocyclic Compounds, Vol. 39, No. 10, 2003

N-(2-PYRIDYL)AMIDES OF 2,4-DIOXOBUTYRIC ACIDS IN REACTIONS WITH DIAZOALKANES

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N-(2-Pyridyl)amides of 4-R-2-alkoxy-4-arylcrotonic acids and 3-alkoxy-3-aroylmethyl-2-oxo-2,3-dihydroimidazo[1,2-a]pyridines have been synthesized by the interaction of N-(2-pyridyl)amides of 4-aryl-2,4-dioxobutyric acids with diazoalkanes. The structure and mechanism of formation of the products are discussed.

Keywords: diazoalkanes, 2-oxo-2,3-dihydroimidazo[1,2-*a*]pyridines, N-(2-pyridyl)amides of 2,4-dioxobutyric acids, intramolecular cyclization.

Previously we reported the unusual cyclization of N-(2-thiazolyl)amides of 4-aryl-2,4-dioxobutyric acids into derivatives of imidazo[1,2-*a*]thiazole under the action of diazomethane [1,2]. As a continuation of investigations on the intramolecular cyclization of heterylamides of 4-aryl-2,4-dioxobutyric acids under the action of diazonucleophiles, the interaction of N-(2-pyridyl)amides of 4-aryl-2,4-dioxobutyric acids **1a-e** with diazomethane and diazoethane has been studied in the present work.

It was established that the reaction of amides **1a-e** with diazomethane forms N-(2-pyridyl)amides of 4-aryl-2-methoxy-4-oxocrotonic acids **2a,b** and 3-aroylmethyl-3-methoxy-2-oxo-2,3-dihydroimidazo[1,2-*a*]-pyridines **3a-e** in yields of 5-8 and 32-48% respectively. Interaction of amides **1a,b,e** with diazoethane leads to N-(2-pyridyl)-amides of 4-aryl-4,5-epoxy-2-ethoxy-2-hexenoic acids **4a,b** in 3% yield and 3-aroylmethyl-3-ethoxy-2-oxo-2,3-dihydroimidazo[1,2-*a*]pyridines **5a-c** in 24-45% yield (see Tables 1 and 2, Scheme 1).

According to the spectral characteristics amides **1a-e** are completely enolized in solution [3,4], and compounds **2a,b** are the products of O-methylation of the enolic hydroxyl of compounds **1a,b**. In the IR spectra of compounds **2a,b** there was an absorption band for the ketonic carbonyl $C_{(4)}$=O at 1670, 1675 cm^{-1}, which is involved in an intramolecular hydrogen bond (IHB) of the H-chelate type in the initial compounds **1a,b**, but in the ^{1}H NMR spectrum of compound **2a** a singlet was observed for the methyl group protons at 3.95 ppm. O-Ethylation of the enolic hydroxyl of amides **1a,e** is also effected in the reaction with diazoethane, but in view of its nucleophilicity, which is greater than for diazomethane, the latter process goes further with attack by a second molecule of diazoethane at the ketonic carbonyl $C_{(4)}$=O of the already alkylated product. In the IR spectra of compounds **4a,b** there was no absorption band for the ketonic carbonyl but the ^{1}H NMR spectra were characterized by a group of signals of complex multiplicity, assigned to the *E*- and *Z*-forms of these compounds (Table 2). The mass spectrum of compound **4a** contains a peak for the molecular ion with *m/z* 324 and intensity

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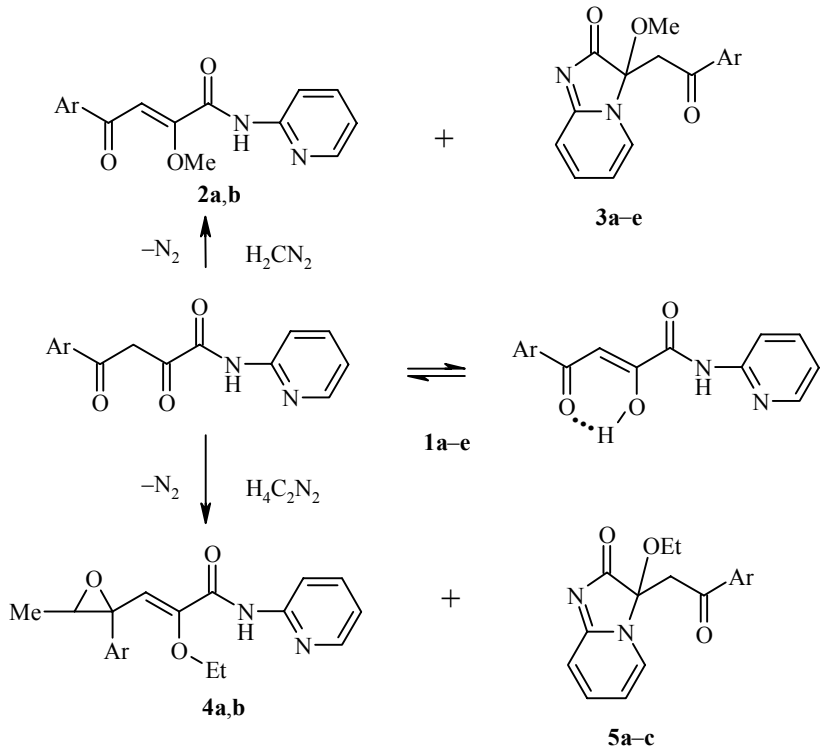
 0009-3122/03/3910-1326$25.00

Scheme 1



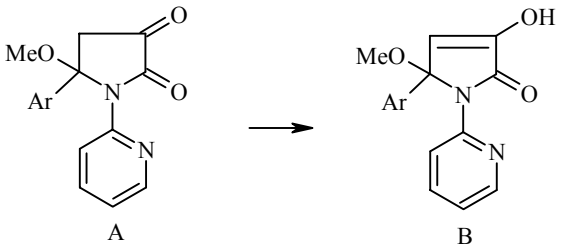
1, 3 a Ar = Ph, **b** Ar = 4-MeC_6H_4, **c** Ar = 4-$MeOC_6H_4$, **d** Ar = 4-ClC_6H_4, **e** Ar = 4-BrC_6H_4; **2 a** Ar = Ph, **b** Ar = 4-MeC_6H_4; **4 a** Ar = Ph, **b** Ar = 4-BrC_6H_4; **5 a** Ar = Ph, **b** Ar = 4-MeC_6H_4, **c** Ar = 4-BrC_6H_4

0.12%, and the following peaks (*m/z*, I_{rel}, %): 295 (0.6) $[M\text{-}C_2H_5]^+$, 231 (9.7) $[M\text{-}NHC_5H_4H]^+$, 203 (8.2) $[M\text{-}OCNHC_5H_4N]^+$, 121 (31.6) $[OCNHC_4H_4N]^+$, 105 (100) $[C_6H_5CO]^+$, 78 (55.4) $[C_5H_4N]^+$, 77 (87.3) $[C_6H_5]^+$, which do not contradict the structure proposed.

According to TLC data up to six reaction products were detected in the reaction mixture, but at any of the amide–diazoalkane ratios studied (1:1, 1:2, 1:4) the main reaction products were the imidazo[1,2-*a*]pyridine derivatives **3a-e**, **5a-c**. The IR spectra of compounds **3** and **5** are characterized by the presence of absorption bands for two carbonyl groups at 1700-1740 and 1650-1700 cm^{-1} and by the absence of an absorption band for the amide NH group. In the ^1H NMR spectra, apart from the signals of the alkoxy group and the aromatic protons, a signal was present for the two protons of the methylene group at the chiral carbon atom of the heterocycle $C_{(3)}$, which depending on the solvent used was resolved as a singlet at 3.66-3.82, a doublet at 3.97-4.25, or a quadruplet at 4.14-4.59 ppm. It should be noted that the methylene protons of the EtO group, connected to the asymmetric $C_{(3)}$ atom in compounds **5a-c**, are diastereotopic and consequently their signals in the ^1H NMR spectra have the form of two quartets at 3.05-3.18 and 3.45-3.58 ppm.

The mass spectrum of compound **3a** contains a peak for the molecular ion with *m/z* 282 (*I* 24%), and the following peaks (*m/z*, I_{rel}, %): 267 (9) $[M\text{-}CH_3]^+$, 205 (7) $[M\text{-}C_6H_5]^+$, 177 (47) $[M\text{-}C_6H_5CO]^+$, 121 (100) $[OCNHC_5H_4N]^+$, 105 (61) $[C_6H_5CO]^+$, 77 (41) $[C_6H_5]^+$, which do not contradict the proposed structure.

The ^{13}C NMR spectrum of compound **3b** contains the following signals (δ, ppm): 21.15 (*p*-$\underline{C}H_3C_6H_4$); 43.4 ($C_{(3)}$–$\underline{C}H_2$); 52.40 ($C_{(3)}$–O$\underline{C}$H3); 92.15 ($C_{(3)}$), 112.40, 116.49, 128.65, 129.65, 134.0, 134.40, 143.40, 144.90 (C arom.); 169.15 ($C_{(9)}$), 182.65 ($C_{(2)}$=O), 193.90 (C=O). The presence in the spectrum of a signal for the carbon atoms of the amide carbonyl of the heterocycle ($C_{(2)}$=O) and the ketonic carbonyl at 182.5 and 193.9 ppm enables rejection of the alternative structure of 5,5-disubstituted tetrahydro-2,3-pyrrolediones (A), in which the ketonic carbonyl is enolized (B), for compound **3b** and compounds **3, 5** [5].



The formation of compounds **3** and **5** probably begins with the protonation of the diazoalkane by the hydrogen atom of the enolic hydroxyl and rearrangement of the 2-pyridylamide fragment into a pyridoneimide with the formation of intermediate C. The nucleophilicity of the "internally" formed NH-nucleophile is greater than the nucleophilicity of the diazoalkane, a second molecule of which may participate in further conversions of the carbonyl substrate, and its attack is directed to the sterically more available and electrophilic $C_{(2)}$ atom. The formation of the imidazole ring is accompanied by rupture of the $C_{(2)}$=$C_{(3)}$ multiple bond, by the elimination of nitrogen, and by migration of a hydrogen atom to the $C_{(3)}$ atom.

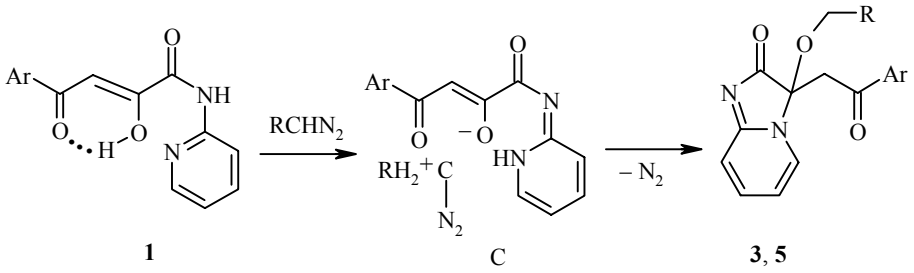


TABLE 1. Characteristics of the Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %				mp, °C*	Yield, %
		C	H	N	Hal		
2a	$C_{16}H_{14}N_2O_3$	68.21 / 68.07	4.94 / 5.00	9.87 / 9.92	—	104-106	8
2b	$C_{17}H_{16}N_2O_3$	68.99 / 68.91	5.40 / 5.44	9.36 / 9.45	—	134-136	5
3a	$C_{16}H_{14}N_2O_3$	68.14 / 68.08	5.03 / 5.00	9.84 / 9.92	—	197.0-197.5 (dec.)	47
3b	$C_{17}H_{16}N_2O_3$	68.87 / 68.91	5.40 / 5.44	9.43 / 9.45	—	201.5-203.0 (dec.)	48
3c	$C_{17}H_{16}N_2O_4$	65.46 / 65.38	5.19 / 5.16	8.89 / 8.97	—	174.5-176.0 (dec.)	43
3d	$C_{16}H_{13}ClN_2O_3$	60.73 / 60.67	4.12 / 4.14	8.78 / 8.84	11.12 / 11.19	207-208 (dec.)	39
3e	$C_{16}H_{13}BrN_2O_3$	53.15 / 53.21	3.65 / 3.63	7.79 / 7.76	22.21 / 22.12	223-224 (dec.)	31
4a	$C_{19}H_{20}N_2O_3$	70.44 / 70.35	6.20 / 6.21	8.57 / 8.64	—	76-78	3
4b	$C_{19}H_{19}BrN_2O_3$	56.64 / 56.59	4.63 / 4.75	6.83 / 6.95	19.94 / 19.81	150-151	3
5a	$C_{17}H_{16}N_2O_3$	68.97 / 68.91	5.46 / 5.44	9.39 / 9.45	—	194-196 (dec.)	43
5b	$C_{18}H_{18}N_2O_3$	69.71 / 69.66	5.89 / 5.85	8.96 / 9.03		187.0-187.5 (dec.)	25
5c	$C_{17}H_{15}BrN_2O_3$	54.47 / 54.42	4.06 / 4.03	7.41 / 7.47	21.38 / 21.30	194-195 (dec.)	45

* Compounds **2a,b** and **4a,b** were recrystallized from hexane, and compounds **3a-e**, **5a-c** from benzene.

TABLE 2. Spectral Characteristics of Compounds **2-5**

Compound	R_f	IR spectrum, ν, cm^{-1}	UV spectrum, λ_{max}, nm (log ε)	Solvent	Chemical shifts, δ, ppm (coupling constants, *J*, Hz)
1	2	3	4	5	6
2a	0.84	1670 (C=O), 1711 (NH<u>CO</u>), 3375 (NH)	209; 229; 312	DMSO-d_6	3.95 (3H, s, CH_3O); 6.82 (1H, s, =CH); 7.42 (9H, m, $5H_{Ph}$, $4H_{Het}$); 9.58 (1H, s, NH)
2b	—	1675 (C=O), 1712 (NH<u>CO</u>), 3382 (NH)	203; 226; 324		—
3a	0.21	1650 (C=O), 1723 (C=O lactam.), 3080 (CH)	251 (4.47), 361 (3.84)	$CDCl_3$	3.12 (3H, s, CH_3O); 3.82 (2H, s, CH_2); 7.51 (9H, m, $5H_{Ph}$, $4H_{Het}$)
				$CDCl_3$ + F_3CCOOH	3.12 (3H, s, CH_3O); 4.25 (2H, d, CH_2, J = 8); 7.52 (9H, m, $5H_{Ph}$, $4H_{Het}$)
				$CDCl_3$ + DMSO-d_6, 1:1	3.22 (3H, s, CH_3O); 4.59 (2H, q, CH_2, J = 6); 7.51 (9H, m, $5H_{Ph}$, $4H_{Het}$)
3b	0.16	1700 (C=O), 1740 (C=O lactam.), 3030 (CH)	257 (4.91), 358 (3.94)	$CDCl_3$	2.32 (3H, s, CH_3); 3.12 (3H, s, CH_3O); 3.75 (2H, s, CH_2); 7.35 (8H, m, $4H_{Ar}$, $4H_{Het}$)
3c	0.16	1670 (C=O), 1712 (C=O lactam.), 3012 (CH)	261 (4.3), 280 (4.24), 361 (3.74)	$CDCl_3$	3.11 (3H, s, CH_3O); 3.71 (2H, s, CH_2); 3.85 (3H, s, <u>CH_3</u>OC_6H_4); 7.22 (8H, m, $4H_{Ar}$, $4H_{Het}$) 3.11 (3H, s, CH_3);
				$CDCl_3$ + F_3CCOOH	3.85 (3H, s, <u>CH_3</u>OC_6H_4); 4.18 (2H, s, CH_2); 7.22 (8H, m, $4H_{Ar}$, $4H_{Het}$)
3d	0.16	1680 (C=O), 1714 (C=O lactam.), 3012 (CH)	256 (4.50), 363 (3.79)	$CDCl_3$	3.08 (3H, s, CH_3O); 3.66 (2H, s, CH_2); 7.38 (8H, m, $4H_{Ar}$, $4H_{Het}$)
				$CDCl_3$ + F_3CCOOH	3.18 (3H, s, CH_3O); 4.16 (2H, s, CH_2); 7.45 (8H, m, $4H_{Ar}$, $4H_{Het}$)
				$CDCl_3$ + DMSO-d_6, 1:1	3.05 (3H, s, CH_3O); 3.97 (2H, d, CH_2, J = 6); 7.55 (8H, m, $4H_{Ar}$, $4H_{Het}$)
				$CDCl_3$ + DMSO-d_6, (1:1) + F_3CCOOH	3.18 (3H, s, CH_3O); 4.53 (2H, q, CH_2, J = 6); 7.60 (8H, m, $4H_{Ar}$, $4H_{Het}$)

TABLE 2 (continued)

1	2	3	4	5	6
3e	0.17	1680 (C=O), 1716 (C=O lactam.), 3012 (CH)	258 (4.57), 362 (3.83)	$CDCl_3$	3.15 (3H, s, CH_3O); 3.78 (2H, s, CH_2); 7.65 (8H, m, $4H_{Ar}$, $4H_{Het}$)
				$CDCl_3 + F_3CCOOH$	3.11 (3H, s, CH_3O); 4.12 (2H, s, CH_2); 7.51 (8H, m, $4H_{Ar}$, $4H_{Het}$)
4a	0.83*	1690 (C=O), 3380 (NH)	237 (4.45), 275 (4.35), 312 (4.08)	$CDCl_3$	1.25 (6H, m, $\underline{CH_3}CH_2$, $\underline{CH_3}CH$); 3.52 (2H, q, $CH_3\underline{CH_2}$, $J = 7$); 4.49 (1H, q, $CH_3\underline{CH}$, $J = 6$); 7.55 (10H, m, $5H_{Ph}$, $4H_{Het}$, =CH); 9.28, 9.41 (1H, two s, 2:3, NH)
4b	0.49*; 0.81	1690 (C=O), 3320 br (NH)	197, 236, 276, 335	$CDCl_3$	1.27 (6H, m, $\underline{CH_3}CH_2$, $\underline{CH_3}CH$); 3.50 (2H, q, $CH_3\underline{CH_2}$, $J = 7$); 4.40 (1H, q, $CH_3\underline{CH}$, $J = 6$); 7.66 (9H, m, $4H_{Ar}$, $4H_{Het}$, =CH); 9.31, 9.58 (1H, two s, 1:4, NH)
5a	0.24	1675 (C=O), 1720 (C=O lactam.), 3080 (CH)	251 (4.43), 362 (3.81)	$CDCl_3$	1.11 (3H, t, CH_3, $J = 8$); 3.05 (1H, q, $CH_3\underline{CH_2}$, $J = 8$); 3.55 (1H, q, $CH_3\underline{CH_2}$, $J = 8$); 3.78 (2H, s, CH_2); 7.55 (9H, m, $5H_{PH}$, $4H_{Het}$)
				$CDCl_3 + F_3CCOOH$	1.14 (3H, t, CH_3, $J = 8$); 3.15 (1H, q, $CH_3\underline{CH_2}$, $J = 8$); 3.50 (1H, q, $CH_3\underline{CH_2}$, $J = 8$); 4.25 (2H, q, CH_2, $J = 4$); 7.63 (9H, m, $5H_{PH}$, $4H_{Het}$)
5b	0.18*	1685 (C=O), 1700 (C=O lactam.), 3045 (CH)	257 (4.61), 362 (3.90)	$CDCl_3$	1.11 (3H, t, $\underline{CH_3}CH_2$, $J = 8$); 2.34 (3H, s, CH_3); 3.06 (1H, q, $CH_3\underline{CH_2}$, $J = 8$); 3.45 (1H, q, $CH_3\underline{CH_2}$, $J = 8$); 3.74 (2H, s, CH_2); 7.33 (8H, m, $4H_{Ar}$, $4H_{Het}$)
				$CDCl_3 + F_3CCOOH$	1.12 (3H, t, $\underline{CH_3}CH_2$, $J = 8$); 2.34 (3H, s, CH_3); 3.09 (1H, q, $CH_3\underline{CH_2}$, $J = 8$); 3.49 (1H, q, CH_3CH_2, $J = 8$); 4.18 (2H, q, CH_2, $J = 3$); 7.55 (8H, m, $4H_{Ar}$, $4H_{Het}$)
5c	0.23*	1670 (C=O), 1710 (C=O lactam.)	257 (4.41), 357 (3.33)	$CDCl_3$	1.10 (3H, t, CH_3, $J = 7$); 3.11 (1H, q, CH_2, $J = 7$); 3.48 (1H, q, CH_2, $J = 7$); 3.71 (2H, s, CH_2); 7.85 (8H, m, $4H_{Ar}$, $4H_{Het}$)
				$CDCl_3 + F_3CCOOH$	1.18 (3H, t, $\underline{CH_3}CH_2$, $J = 8$); 3.18 (1H, q, CH_2, $J = 8$); 3.58 (1H, q, CH_2, $J = 8$); 4.14 (2H, q, CH_2, $J = 4$); 7.80 (8H, m, $4H_{Ar}$, $4H_{Het}$)

*R_f values were determined in ethanol, other R_f values were determined in acetone.

O-Alklylation of the enolic hydroxyl and cyclization are probably coordinated processes since O-methyl derivatives of 2-pyridylamides **2a,b** are not cyclized by the action of diazoalkanes.

EXPERIMENTAL

The IR spectra were obtained on a UR-20 spectrometer in nujol mulls, and the ^{1}H NMR spectra on a Bruker WR-80 SY instrument (80 MHz) for solutions in DMSO-d_6 and $CDCl_3$, internal standard was TMS. The mass spectra were taken on a MX-1320 instrument, ionizing voltage was 70 eV. The UV spectra were recorded on a SF-46 spectrophotometer for solutions in ethanol. TLC was carried out on Silufol UV-254 plates in acetone–alcohol.

N-(2-Pyridyl)amides of 4-Aryl-2-methoxy-4-oxocrotonic Acids (2a,b), 3-(benzoylmethyl)-3-methoxy-2-oxo-2,3-dihydroimidazo[1,2-*a*]pyridines (3a-e). A solution of diazomethane (10 mmol) in ether (15 ml) was added to a solution of compound **1a-e** (10 mmol) in benzene (30 ml). The reaction mixture was stirred for 3 h at -5 to 0°C, cooled, and the solid product **3a-e** filtered off. The filtrate was evaporated, and product **2a,b** isolated by recrystallization of the residue.

N-(2-Pyridyl)amides of 4-Aryl-4,5-epoxy-2-ethoxy-2-hexenoic Acids (4a,b), 3-Aroylmethyl-3-ethoxy-2-oxo-2,3-dihydroimidazo[1,2-*a*]pyridines (5a-c). A solution of diazoethane (20 mmol) in ether (30 ml) was added to a solution of compound **1a,b,e** in benzene (30 ml). The reaction mixture was stirred for 3 h at -5 to 0°C, cooled, and the product **5a-c** filtered off. The filtrate was evaporated, and the residue of product **4a,b** was recrystallized.

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