Improvement in the Synthesis of *N,N'*-Diacyl-1,2-di(4-pyridyl)ethylenediamines

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A better synthetic route to pharmacologically active *N,N'*-diacyl-1,2-di(4-pyridyl)ethylenediamines is described.

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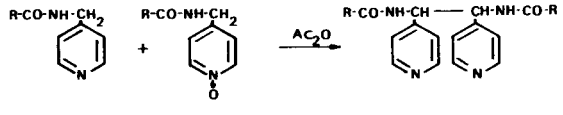
Earlier work in these laboratories has led to the discovery of the synthesis of *N,N'*-diacyl-1,2-di(4-pyridyl)ethylenediamines **3** by reaction of *N*-(4-pyridylmethyl)amide *N*-oxides **2** with acetic anhydride [2,3]. These compounds show analgesic and antiinflammatory activity. The study on the structure-activity relationships was object of a paper [4].

Hamana described that quinoline *N*-oxide reacted with some active methylene compounds in the presence of acetic anhydride to give 2-substituted quinolines, accompanied by the deoxygenation of the *N*-oxide function. Thus the reaction can be extended to pyridine *N*-oxides [5].

We now report a more satisfactory novel procedure for the synthesis of **3**, based upon the reaction of *N*-(4-pyridylmethyl)amide **1** with its *N*-oxide **2** in presence of acetic anhydride.

Figure 1



Heating to 70° a mixture of **1** (1 equivalent) with **2** (1 equivalent) and acetic anhydride (9 equivalents) for 3 hours furnished the diacylethylenediamines **3** in 90-100% yield (see Table). The mechanism for the formation of **3** involves the initial formation of acetoxy derivative **4**, from the *N*-oxide **2** with acetic anhydride [6]. Evidence supporting the intermediacy of **4** in the conversion of **1** to **3** is offered by reaction of **4** with **1a** in DMF to form **3a** in the same yield.

Table 1

N,N'-Diacyl-1,2-di(4-pyridyl)ethylenediamines

Product	R	Yield (%)	Mp °C	Ref	Yield (%)	Mp °C
3a	3,5-$(CH_3)_2$-C_6H_3	42	336-338	[2]	98	338
3b	CH_3	40	308	[3]	90	308
3c	$(CH_3$-CH_2-$CH_2)_2CH$	43	339	[3]	95	340
3d	C_6H_5-CH_2	22	312	[3]	98	311
3e	C_6H_5	26	298	[3]	95	298
3f	4-CH_3-C_6H_4	44	291	[3]	96	292
3g	3-CH_3-C_6H_4	41	275	[3]	96	275
3h	2-CH_3-C_6H_4	39	339	[3]	95	337
3i	4-tC_4H_9-C_6H_4	70	305	[3]	100	305
3j	4-CH_3-O-C_6H_4	44	299	[3]	92	298
3k	4-CH_3-SO_2-C_6H_4	64	287	[3]	96	287
3l	4-NO_2-C_6H_4	54	312	[3]	98	312
3m	4-C_6H_5-C_6H_4	40	326	[3]	97	325
3n	4-Cl-C_6H_4	39	323	[3]	98	324
3o	3-Cl-C_6H_4	38	297	[3]	92	297
3p	2-Cl-C_6H_4	39	308	[3]	96	308
3q	3,5-Cl_2-C_6H_3	38	275	[3]	99	277
3r	4-F-C_6H_4	33	288	[3]	97	289
3s	4-CF_3-C_6H_4	38	316	[3]	96	316

EXPERIMENTAL

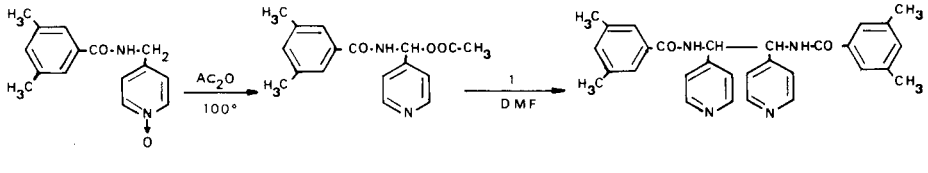
N,N'-Diacyl-1,2-di(4-pyridyl)ethylenediamines **3**. General Procedure.

A mixture of *N*-(4-pyridylmethyl)amide (0.01 mole), *N*-(4-pyridylmethyl)amide *N*-oxide (0.01 mole) and 7 ml of acetic anhydride was heated to 70° in a water bath for 3 hours after which the precipitate was collected, washed with ethyl acetate and recrystallized to give **3**.

Ethylenediamine **3a** From **4**.

A solution of 2.4 g (0.01 mole) of *N*-(4-pyridylmethyl)-3,5-dimethylbenzamide and 2.9 g (0.01 mole) of *N*-[(α-acetoxy)-4-pyridylmethyl]-3,5-dimethylbenzamide in 5 ml of dimethylformamide was heated to 70° in a water

Figure 2



bath for 3 hours. The precipitate was collected, washed with ethyl acetate and recrystallized in DMF to afford **3a**, yield 4.7 g (98%).

REFERENCES AND NOTES

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