BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 46, 3277—3280 (1973)

Reactions of *N*-Acylaminoacetamidine with 1,3-Bifunctional Compounds

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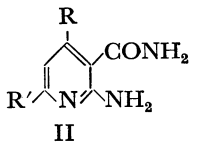
(Received May 4, 1973)

The reactions of *N*-benzoylaminoacetamidine(IIIa) and *N*-benzyloxycarbonylaminoacetamidine(IIIb) with various 1,3-bifunctional compounds were investigated. Both IIIa and IIIb were found to react with acetylacetone to produce 2-amino-3-benzoylamino-4,6-dimethylpyridine and 2-amino-3-benzyloxycarbonylamino-4,6-dimethylpyridine, respectively. On the other hand, IIIa reacted with ethyl acetoacetate or diketene to produce 2-(*N*-benzoylaminomethyl)-4-hydroxy-6-methylpyrimidine. Reaction of IIIb with malononitrile gave 1-amino-2-(*N*-benzyloxycarbonylaminoethylidene)malononitrile.

Amidines and 1,3-bifunctinal compounds react generally to form pyrimidines, and rarely to form another heterocyclic ring system. The reaction of malonamideamidine(I) with β-ethoxyacrolein diethylacetal or 1,3-dicarbonyl compounds has been reported[1,2] to produce 2-aminonicotinamide derivatives (II).

$H_2NCOCH_2C(=NH)NH_2$

I



II

Goldberg and Kelly[3] reported that the reaction product between *N*-benzoylaminoacetamidine(IIIa) and acetylacetone was 2-(*N*-benzoylaminomethyl)-4,6-dimethylpyrimidine(IVa) on the basis of elemental analysis only. We have followed their procedure to prepare IVa and obtained a product having an empirical formula $C_{14}H_{15}ON_3$ and the same melting point as described. However, the IR spectrum of the product

1) A. Dornow and K. Peterlein, *Chem. Ber.*, **82**, 257 (1949).
2) A. Dornow and E. Neuse, *ibid.*, **84**, 296 (1951).
3) A. A. Goldberg and W. Kelly, *J. Chem. Soc.*, **1947**, 1372.

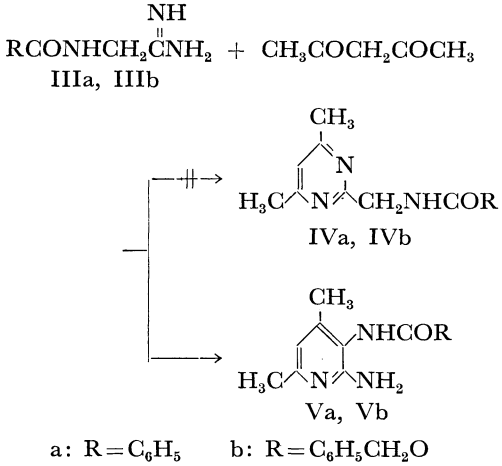
Table 1. Reaction of IIIa[a] with acetylacetone

Reaction	Solvent	Reaction		Alkali	Molar ratio of IIIa HCl : alkali	Yield of Va (%)
		Temp. (°C)	Time (hr)			
1[b]	C_2H_5OH	reflux	4	K_2CO_3	1 : 1	23
2	C_2H_5OH	reflux	4	K_2CO_3	1 : 2.5	17
3	C_2H_5OH	reflux	9	K_2CO_3	1 : 1	20
4	C_2H_5OH	reflux	15	K_2CO_3	1 : 1	11
5	C_2H_5OH	reflux	4	C_2H_5ONa	1 : 0.1[c]	20
6	DMF	70	4	K_2CO_3	1 : 2	21
7	DMF	90	4	K_2CO_3	1 : 2	18

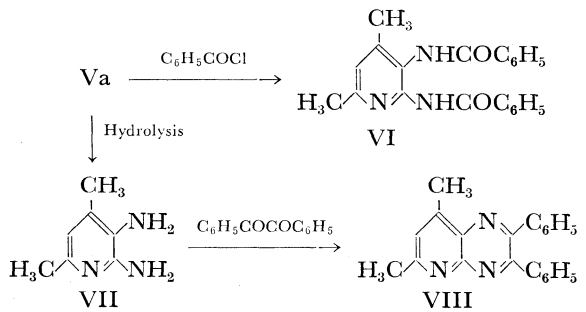
a) Used in the form of hydrochloride except in Reaction 5.
b) The same conditions as given in Ref. 3.
c) Ratio of free IIIa : alkali.

showed absorptions attributed to =NH, $-NH_2$, and an amide carbonyl group. Additional information was obtained from the NMR spectrum. There were singlet peaks at τ 0.50(1H) and τ 4.37(2H) which disappeared with the addition of deuterium oxide, and two at τ 7.73(3H) and τ 7.93(3H) due to unequivalent two methyl groups.

On the basis of spectral results it is reasonable to consider that the reaction proceeded, as in the case of formation of II from I, to form 2-amino-3-benzoylamino-4,6-dimethylpyridine(Va).



In order to collect chemical evidences on the assigned structure of Va, the following reactions were carried out. Treatment of Va with benzoyl chloride led to 2,3-dibenzoylamino-4,6-dimethylpyridine(VI). Hydrolysis of Va yielded 2,3-diamino-4,6-dimethylpyridine(VII) which condensed with benzil to produce 2,3-diphenyl-6,8-dimethylpyrido[2,3-*b*]-pyrazine(VIII). These properties can be explained satisfactorily only with Va and do not seem to occur with IVa.



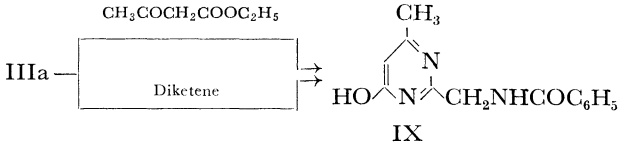
In order to learn whether the pyrimidine derivative (IVa) could be formed by the present reaction and for the purpose of improving the yield of Va, the reaction was carried out under various conditions (Table 1). All efforts to improve the yield of Va were unsuccessful. This can be attributed to the facile hydrolysis of free amidine(IIIa) in alkaline medium which competes with the formation of Va. In fact, a considerable amount of *N*-benzoylaminoacetamide was obtained as a by-product in each experiment. The reaction at room temperature, in benzene, or in acetic acid in the presence of sodium acetate gave no Va.

The reaction of *N*-benzyloxycarbonylaminoacetamidine(IIIb) with acetylacetone in ethanol in the presence of sodium ethoxide proceeded in a similar way affording 2-amino-3-benzyloxycarbonylamino-4,6-dimethylpyridine(Vb) in a poor yield. The assignment of structure Vb was based on its composition, IR and NMR spectra.

The reactivity of the methylene groups in IIIa and IIIb is considered to be much lower than that of the methylene group in I. It is notable that the methylene group in III participated in the ring formation.

Next, the reaction of IIIa with ethyl acetoacetate in the presence of sodium hydroxide was studied. The product, having an empirical formula $C_{13}H_{13}O_2N_3$, is soluble in aqueous sodium hydroxide and devoid of primary amino absorption in the IR spectrum. The doublet centered at τ 5.65 (2H, J=2.8 Hz) in the NMR spectrum assigned to methylene protons changed to a singlet, the triplet at τ 1.10(1H, J=2.8 Hz) disappearing with the addition of deuterium oxide. This indicates that the methylene protons are coupled with the =NH of the neighboring amide group. Elemental and spectrometric analyses identified the product as 2-(*N*-benzoylaminomethyl)-4-hydroxy-6-methylpyrimidine (IX).

As an alternative synthesis of IX, diketene was made to react with IIIa in ethanol at 0 °C. The product was identical with that previously prepared.



The reaction of IIIa with other 1,3-bifunctional compounds was also studied. The following reagents were used as 1,3-bifunctional compounds, *i.e.*, benzoylacetone, dibenzoylmethane, ethyl dimethylmalonate, methyl acrylate, and acetylacetaldehyde dimethylacetal. The reactions were carried out in ethanol at 45 °C for 2 days or under reflux for 4 hours in the presence of potassium carbonate or sodium ethoxide. All trials to isolate the expected product were unsuccessful.

Amidine IIIa is known to react with malononitrile and ethyl cyanoacetate to yield 1-amino-2-(*N*-benzoylaminoethylidene)malononitrile and ethyl 1-amino-2-(*N*-benzoylaminoethylidene)cyanoacetate, respectively.[3] A similar condensation of ethyl cyanoacetate with formamidine or benzamidine in the absence of alkali was reported.[4] We have now found that the reaction of IIIb with malononitrile proceeds analogously, 1-amino-2-(*N*-benzyloxycarbonylaminoethylidene)malononitrile(X) being obtained.

$$\text{IIIb} + CH_2(CN)_2 \rightarrow C_6H_5CH_2OCONHCH_2\underset{\displaystyle NH_2}{\overset{\displaystyle |}{C}}{=}C(CN)_2$$

X

Experimental

All melting points were uncorrected. The NMR spectra were recorded at 60 MHz using tetramethylsilane as an internal standard.

2-Amino-3-benzoylamino-4,6-dimethylpyridine(Va). To a solution of 9 g (90 mmol) of acetylacetone in 75 ml of ethanol was added 15 g (70 mmol) of IIIa hydrochloride[3] and 10 g (72 mmol) of potassium carbonate, and refluxed for 4 hr with stirring. The reaction mixture was concentrated and the residue was dissolved in 70 ml of 10% hydrochloric acid. Insoluble *N*-benzoylaminoacetamide [mp 183 °C (lit,[3] 186 °C), 5 g (40%)] was removed by filtration, the filtrate being made alkaline with 10% aqueous sodium hydroxide. Precipitates were collected and recrystallized from methanol to give colorless needles of Va, mp 197—198 °C, 3.9 g (23%).

Found: C, 69.57; H, 6.51; N, 17.71%. Calcd for $C_{14}H_{15}ON_3$: C, 69.69; H, 6.27; N, 17.42%. IR(KBr) cm^{-1}: 3425, 3300, 3180, 1635, 1530. NMR ($CDCl_3$)τ: 0.50 (s, 1H), 1.80—2.67 (m, 5H), 3.55 (s, 1H), 4.37 (s, 2H), 7.73 (s, 3H), 7.93 (s, 3H).

2,3-Dibenzoylamino-4,6-dimethylpyridine(VI). To a solution of 1.2 g (5 mmol) of Va in 20 ml of 10% hydrochloric acid was added 0.7 g (5 mmol) of benzoyl chloride under ice cooling. Aqueous sodium hydroxide (10%) was added dropwise until the solution became alkaline. The precipitates were collected and recrystallized from dimethylformamide to give white powder of VI, mp 223—225 °C, 1.1 g (64%).

Found: C, 73.01; H, 5.61; N, 12.27%. Calcd for $C_{21}H_{19}O_2N_3$: C, 73.03; H, 5.54; N, 12.17%. IR(KBr) cm^{-1}: 3215, 1653, 1532. NMR (DMSO-d_6)τ: 1.77—2.63 (m, 10H), 2.90 (s, 1H), 5.87 (s, 2H) 7.54 (s, 3H), 7.71 (s, 3H).

2,3-Diamino-4,6-dimethylpyridine(VII). A solution of 2 g (8.3 mmol) of Va in 30 ml of 10% hydrochloric acid was heated under reflux for 6 hr. On cooling, benzoic acid which separated out was removed by filtration. The filtrate was treated with charcoal, concentrated to *ca.* 10 ml, and then made strongly alkaline with 10% aqueous sodium hydroxide to give crystalline substance. Recrystallization from water afforded colorless needles of VII, mp 156—158 °C, 0.9 g (79%).

Found: C, 61.59; H, 7.99; N, 30.32%. Calcd for $C_7H_{11}N_3$: C, 61.29; H, 8.08; N, 30.63%. IR(KBr) cm^{-1}: 3380, 3320. NMR (DMSO-d_6)τ: 3.81 (s, 1H), 4.74 (s, 2H), 5.86 (s, 2H), 7.88 (s, 3H), 8.00 (s, 3H).

2,3-Diphenyl-6,8-dimethylpyrido[2,3-b]pyrazine(VIII). A mixture of 0.69 g (5 mmol) of VII and 1.05 g (5 mmol) of benzil was heated for 30 min, the temperature being maintained at 120 °C. The reactants melted first and solidified again. Recrystallization from a mixture of ethanol and benzene gave colorless prisms of VIII, mp 189—190 °C, 1.4 g (89%). Found: C, 81.19; H, 5.56; N, 13.27%. Calcd for $C_{21}H_{17}N_3$: C, 81.00; H, 5.50; N, 13.50%. IR (KBr) cm^{-1}: 3030, 1590, 770, 700. NMR($CDCl_3$)τ: 2.23—2.87 (m, 10H and 1H of CH), 7.20 (s, 6H).

2-(N-Benzoylaminomethyl)-4-hydroxy-6-methylpyrimidine(IX). An ethanol solution of sodium ethoxide prepared from 0.7 g (30 mmol) of sodium and 30 ml of ethanol was added to a solution of 6.4 g (30 mmol) of IIIa hydrochloride in 20 ml of ethanol under ice cooling and the precipitated sodium chloride was removed by filtration. To the filtrate was added 3.9 g (30 mmol) of ethyl acetoacetate. This was transferred to an evaporating dish and evaporated to dryness in a desiccator over sulfuric acid. The residue was added to a mixture of 10 ml of 20% aqueous sodium hydroxide and 30 ml of ethanol, and stirring was continued at room temperature for 2 days. The reaction mixture was concentrated *in vacuo* and 20 ml of water was added. The water-insoluble substance was removed by filtration, and filtrate was neutralized with 5% hydrochloric acid to afford the precipitate. Recrystallization from dimethylformamide gave colorless needles of IX, mp 241—242 °C, 2.1 g (29%).

Found: C, 63.89; H, 5.26; N, 17.08%. Calcd for $C_{13}H_{13}O_2N_3$: C, 64.19; H, 5.38; N, 17.29%. IR(KBr) cm^{-1}: 3300, 1633. NMR (DMSO-d_6)τ: 1.10 (t, 1H), 2.1—2.5 (m, 5H), 3.93 (s, 1H), 5.65 (d, 2H), 6.67 (s, 1H), 7.87 (s, 3H).

Reaction of IIIa with diketene. A solution of IIIa (30 mmol) in ethanol was prepared by the same procedure as in the preceding experiment. To this was added dropwise 2.6 g (30 mmol) of diketene at 0 °C. Crystals began to separate out after 30 min. The reaction mixture was stirred at room temperature for 1 day. Precipitates were collected and recrystallized from dimethylformamide to give 2.2 g (32%) of IX, mp 241—242 °C. Found: C, 63.96; H, 5.30; N, 17.44%. Spectral data were identical with those obtained in the preceding experiment.

N-Benzyloxycarbonylaminoacetamidine(IIIb) hydrochloride. To a solution of ammonia in ethanol (50 ml, 15% by wt) was added 10 g (37 mmol) of ethyl imino(*N*-benzyloxycarbonylamino)acetate hydrochloride[5] and stirred for 1 hr. The resulting solution, after being allowed to stand at room temperature for 2 days, was concentrated in a desiccator over sulfuric acid. Recrystallization of the residue from acetonitrile gave colorless plates of IIIb hydrochloride, mp 112—113 °C (lit,[5] 78 °C), 5.5 g (62%). Found: C, 48.93; H, 5.52; N, 17.48%. Calcd for $C_{10}H_{14}O_2N_3Cl$: C, 49.39; H. 5.79; N, 17.24%. IR(KBr) cm^{-1}: 3500—2700, 1690, 1525. NMR(DMSO-d_6)τ: 0.87 (b.s, 4H), 2.17 (b.s, 1H), 2.63 (s, 5H), 4.90 (s, 2H), 5.92 (d, 2H).

Reaction of IIIb with acetylacetone. To an ethanol solution of sodium ethoxide prepared from 0.76 g (33 mmol) of

4) G. W. Kenner, B. Lythgoe, A. R. Todd, and A. Topham, *J. Chem. Soc.*, **1943**, 388.

5) M. Mengelberg, *Chem. Ber.*, **89**, 1185 (1956).

sodium and 30 ml of ethanol was added a solution of 6.8 g (28 mmol) of IIIb hydrochloride in 30 ml of ethanol under ice cooling. After removing sodium chloride 3.6 g (36 mmol) of acetylacetone was added and refluxed for 4 hr and then concentrated. To the residue was added 50 ml of chloroform. The crystal, insoluble in chloroform, was collected and recrystallized from ethanol to give colorless needles of *N*-benzyloxycarbonylaminoacetamide, mp 133—134 °C, 2.4 g (41%).

Found: C, 57.40; H, 6.05; N, 13.70%. Calcd for $C_{10}H_{12}O_3N_2$: C, 57.68; H, 5.81; N, 13.45%. IR(KBr) cm^{-1}: 3380, 3315, 3180, 1690, 1655, 1535.

The chloroform solution was concentrated and the residue was subjected to column chromatography on alumina and eluted with ethyl acetate to afford Vb. Recrystallization from a mixture of benzene and ligroin gave colorless needles, mp 162—163 °C, 1.0 g (13%). Found: C, 66.51; H, 6.19; N, 15.41%. Calcd for $C_{15}H_{17}O_2N_3$: C, 66.40; H, 6.31; N, 15.49%. IR(KBr) cm^{-1}: 3450, 3300, 3180, 1700, 1617, 1602. NMR($CDCl_3$)τ: 2.71 (s, 5H), 3.13 (b.s, 1H; exchanged with D_2O), 3.67 (s, 1H), 4.87 (s, 2H), 5.27 (s, 2H; exchanged with D_2O), 7.79 (s, 3H), 7.99 (s, 3H).

*1-Amino-2-(*N*-benzyloxycarbonylaminoethylidene)malononitrile (X).* A solution of IIIb (10 mmol) in 20 ml of ethanol containing sodium ethoxide (2 mmol) was prepared by a similar procedure to that in the preceding experiment. To this solution was added 0.66 g (10 mmol) of malononitrile and refluxed for 30 min. After cooling to room temperature, crystals which separated out were recrystallized from ethanol to give colorless needles of X, mp 169—170 °C, 1.5 g (62%). Found: C, 60.68; H, 4.46; N, 22.13%. Calcd for $C_{13}H_{12}O_2N_4$: C, 60.93; H, 4.72; N, 21.86%. IR(KBr) cm^{-1}: 3400, 3350, 2220, 2190, 1715, 1650, 1548. NMR (DMSO-d_6)τ: 1.33 (b.s, 1H), 1.57 (b.s, 1H), 2.61 (b.s, 1H), 2.63 (s, 5H), 4.93 (s, 2H), 5.98 (d, 2H).