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Formation of 1,3-Dianions of 2- and 3-Acetamidopyridines by Means of *n*-Butyllithium. Condensations with Carbonyl Compounds and Nitriles.[1]

I. T. BARNISH, CHARLES R. HAUSER,

Department of Chemistry, Duke University, Durham, N. C. 27706

AND JAMES F. WOLFE

Department of Chemistry, Virginia Polytechnic Institute, Blacksburg, Virginia 24061

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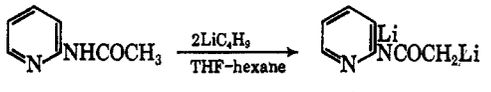
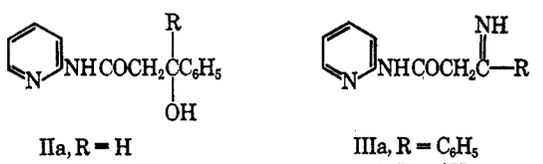
As an extension of our recent method for effecting condensations at the α carbon of acetanilide,[2] we have found that 2- and 3-acetamidopyridines undergo α metalation, as well as N metalation, with excess *n*-butyllithium to form the corresponding dilithioamides, as evidenced by condensations at the terminal position with electrophilic compounds to give C derivatives. Thus, 2-acetamidopyridine (I) was converted into dilithioamide I″, which underwent addition reactions with benzaldehyde, benzophenone, and benzonitrile, and benzoylation with methyl benzoate, to afford IIa, IIb, IIIa, and IV, respectively. Also, I″ was condensed with acetonitrile to give IIIb, but the yield was low presumably because of predominant ionization of an α hydrogen of the nitrile by I″.



I I″



IIa, R = H; b, R = C_6H_5 IIIa, R = C_6H_5; b, R = CH_3

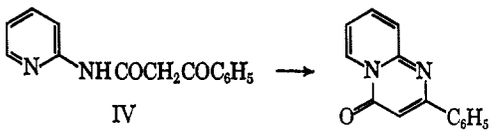
Attempts to effect acid-catalyzed conversions of adducts IIa–b into the corresponding unsaturated and cyclic products, similar to those previously obtained from the benzophenone adduct of acetanilide,[2] were unsuccessful; in the reaction of IIa with cold sulfuric acid, cinnamic acid was obtained. Imine IIIa was hydrolyzed to give the β-ketoamide IV, which was also prepared by the known method from 2-aminopyridine and ethyl benzoylacetate.[3]

(1) Supported at Duke University by Public Health Service Research Grant No. CA-04455 from the National Cancer Institute, and at Virginia Polytechnic Institute by Public Health Service Research Grant No. GM 14340 from the National Institute of General Medical Sciences.

(2) R. L. Gay and C. R. Hauser, *J. Amer. Chem. Soc.*, **89**, 1647 (1967).

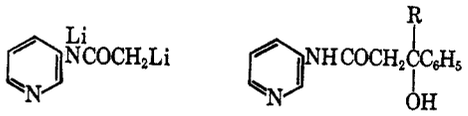
(3) O. Seide, *Ber.*, **58**, 352 (1925).

In the benzoylation of I″, the yield of IV was 56% employing 2 molecular equiv of I″ to one of the ester, but only 30% using molecular equivalents of two reactants; under the latter condition, about half of I″ was presumably neutralized in converting the monolithio salt of IV into its dilithio salt.[4] In connection with identification, β-ketoamide IV was cyclized by means of sulfuric acid to form the rearranged pyrido pyrimidone V.

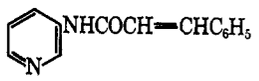


IV V

Similarly, 3-acetamidopyridine was converted by *n*-butyllithium into dilithioamide VI″, which was condensed with benzaldehyde and benzophenone to form adducts VIIa and VIIb, respectively. In contrast to the isomeric adduct IIa, VIIa underwent dehydration with cold sulfuric acid to form the unsaturated amide VIII, which was independently synthesized from 3-aminopyridine and cinnamoyl chloride.



VI″ VIIa, R = H; b, R = C_6H_5



VIII

Experimental Section

Infrared spectra were measured either as mulls in Nujol and hexachlorobutadiene (Perkin Elmer spectrophotometer-Model 137) or as solutions in chloroform (Beckman IR-5A spectrophotometer). Microanalyses were carried out by Jannsen Pharmaceutica, Beerse, Belgium, and also by Galbraith Laboratories, Knoxville, Tenn. Melting points were recorded on a Thomas-Hoover capillary melting point apparatus and are uncorrected unless otherwise stated.

Preparation of 1,3-Dilithio Salt I″.—This was effected by adding, during 10–15 min, a slight excess of 2 molecular equiv of a *ca.* 1.6 M solution of *n*-butyllithium in hexane[5] to a stirred solution of 2-acetamidopyridine in dry tetrahydrofuran (THF) at 0° under nitrogen. Addition of the first molecular equivalent of *n*-butyllithium afforded an amber solution which became reddish orange toward the end of the addition. The resulting solution was then stirred for 15–30 min before addition of the appropriate electrophilic compound.

Addition Reaction of I″ with Benzaldehyde.—Freshly distilled benzaldehyde (5.3 g, 0.05 mol) was added during 3 min to the dilithioamide solution prepared from 2-acetamidopyridine (6.8 g, 0.05 mol), THF (100 ml), and *n*-butyllithium in hexane (66.7 ml). The resulting turbid, pale yellow solution was stirred at 0° for 0.5 hr and then poured into stirred water (100 ml) to furnish a cream precipitate which quickly dissolved. The dark yellow organic layer was combined with an ether extract (50 ml) of the almost colorless aqueous layer and allowed to evaporate thus affording a mixture of a brownish orange oil together with a yellow solid. This mixture was dissolved in boiling toluene and, on cooling, the toluene solution deposited the carbinol-amide IIa (6.68 g, 55%) as a pale cream solid, mp 105.5–106.5°. Recrystallization (chilling) from acetonitrile provided an analytical

(4) See C. R. Hauser, F. W. Swamer, and J. T. Adams, "Organic Reactions," **8**, 59 (1954).

(5) Used as supplied by Foote Mineral Co., Exton, Pa.

sample as colorless prisms: mp 107.5–109°; ν_{max} (Nujol) 3220 broad (OH and NH), 1670 (C=O), 1430, 1153, 1051, 965, 776, 756, 738, 726, and 692 cm^{-1}.

Anal. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.40; H, 5.83; N, 11.56. Found: C, 69.10; H, 5.74; N, 11.53.

Addition Reaction of I″ with Benzophenone.—A solution of benzophenone (4.55 g, 0.025 mol) in THF (30 ml) was added during 5 min to the dilithioamide solution prepared from 2-acetamidopyridine (3.40 g, 0.025 mol), THF (100 ml), and *n*-butyllithium in hexane (36 ml). The resulting turbid yellow solution was stirred at room temperature for 1 hr and then poured into stirred water (100 ml). Most of the THF was allowed to evaporate and the resulting mixture, which contained a pale yellow solid, was extracted with a 1:1 mixture of ether and ethyl acetate. The dried (Na_2SO_4) extracts were evaporated and the solid residue crystallized from methanol to provide the carbinol–amide IIb (4.40 g, 55%) as colorless needles, mp 172–174°. Recrystallization from methanol raised the mp to 174–175° cor. The infrared spectrum ($CHCl_3$) showed bands at ν_{max} 3440–3280 (OH and NH), 1680 (C=O), 1600 shoulder, 1580 1520, 1440, 1300, 1150, 1060. 1010, 1000, and 692 cm^{-1}.

Anal. Calcd for $C_{20}H_{18}N_2O_2$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.37; H, 5.98; N, 8.92.

Reaction of Carbinol–Amide IIa with Sulfuric Acid.—The carbinol–amide IIa (1.0 g) dissolved during *ca.* 1.5 hr in concentrated sulfuric acid at 0° to give a reddish orange solution which was then poured into stirred ice and water (100 g). The resulting white precipitate was collected, dried, and extracted with two 50-ml portions of boiling hexane. On cooling, the combined hexane solutions deposited cinnamic acid as colorless leaves (0.37 g, 61%), mp 134–135°. The infrared spectrum was identical with that of an authentic sample of cinnamic acid, and the melting point was not depressed on admixture.

Benzoylation of I″ with Methyl Benzoate.—Freshly distilled methyl benzoate (1.70 g, 0.0125 mol) was added during 10 sec to the dilithioamide solution prepared from 2-acetamidopyridine (3.40 g, 0.025 mol), THF (50 ml), and *n*-butyllithium in hexane (33.3 ml). The yellow suspension obtained was stirred at 0° for 0.5 hr, then poured into stirred water (50 ml) to provide a pale yellow suspension. The latter was acidified with glacial acetic acid and neutralized ($NaHCO_3$); then the organic layer was combined with an ether extract (50 ml) of the aqueous layer. Evaporation of the combined organic solutions furnished a yellow oil containing a small amount of yellow solid. Repeated trituration of this mixture with 50-ml portions of ether gave the crude β-ketoamide IV as a pale yellow solid (total 1.68 g, 56%). Crystallization (chilling) from acetonitrile afforded IV as pale cream needles (1.29 g, 43%), mp 108.5–109.5°. Colorless needles, mp 110–110.5° (lit.[3] 111–112°), were obtained by recrystallization from hexane–benzene (charcoal): ν_{max} (Nujol) 3200 (NH), 1640 shoulder (C=O), 1625 (C=O), 1575, 1300, 1190, 1154, 995, 787, 764, 712, and 683 cm^{-1}.

The β-ketoamide IV was also prepared from 2-aminopyridine and ethyl benzoylacetate by the known method[3] with slight modification of the work-up procedure. The product (40%) crystallized from carbon tetrachloride as pale cream needles (30%), mp 107.5–108.5°. After recrystallization from acetonitrile, the melting point and mixture melting point was 110–111° (lit.[3] 111–112°). The infrared spectra of both samples were identical.

Addition Reaction of I″ with Benzonitrile.—Benzonitrile (5.15 g, 0.05 mol) was added during 3 min to the dilithioamide solution prepared from 2-acetamidopyridine (6.8 g, 0.05 mol), THF (100 ml), and *n*-butyllithium in hexane (66.7 ml). The resulting dark red solution was stirred at 0° for 45 min during which time it became orange and somewhat cloudy; it was then poured into stirred water (100 ml) and the orange organic layer was combined with an ether extract (100 ml) of the yellow aqueous layer. Evaporation of the combined organic solutions gave an orange oil which, by successive trituration with ether, provided a yellow solid (2.60 g) that was rendered colorless by washing with ether. Crystallization from hexane–benzene afforded imine IIIa (2.09 g) as colorless plates, mp 143–144°.

Evaporation of the combined ether solutions from the trituration furnished a tarry orange material which gave a further crop (2.90 g) of the pure imine on crystallization from hexane–benzene–chloroform; thus the total yield of pure imine IIIa was 5.09 g (43%): ν_{max} (Nujol) 3410 (NH), 3300 (NH), 3300 (NH), 1645 (C=O), 1560, 1430, 1300, 1177, 990, 767, 750, 699, and 690 cm^{-1}.

Anal. Calcd for $C_{14}H_{12}N_2O$: C, 70.27; H, 5.48; N, 17.56. Found: C, 70.03; H, 5.42; N, 17.77.

Hydrolysis of Imine IIIa.—Imine IIIa (2.0 g) dissolved in concentrated sulfuric acid (20 ml) at 0° during *ca.* 0.5 hr to form an almost colorless solution; initially there was a vigorous reaction which quickly subsided. The solution was maintained at 0° for a further 2.5 hr, then poured into stirred ice and water (300 g). The resulting pale yellow solution, on basification with aqueous ammonia solution (29.5%), yielded a gummy pale yellow precipitate. The mixture was extracted with two 100-ml portions of chloroform and the combined chloroform extracts were evaporated to furnish an almost quantitative yield (2.00 g) of the crude ketoamide IV. The latter was obtained as colorless needles, mp and mmp 109–110°, by crystallization from hexane–benzene. Its infrared spectrum was identical with those of IV prepared by the other methods (see above).

Cyclization of Ketoamide IV.—This was effected as previously[3] to afford the crude pyrido pyrimidone V (26%). Crystallization from cyclohexane gave colorless needles (20%): mp 149.5–150° (lit.[3] 151°); ν_{max} (Nujol) 1670 (C=O), 1630 (C=C), 1135, 826, 778, 759, 692, and 671 cm^{-1}.

Anal. Calcd for $C_{14}H_{10}N_2O$: C, 75.65; H, 4.54; N, 12.61. Found: C, 75.78; H, 4.62; N, 12.49.

Reaction of I″with Acetonitrile.—Dry, freshly distilled acetonitrile (0.90 g, 0.022 mol) was added all at once to the dilithioamide solution prepared from 2-acetamidopyridine (2.72 g, 0.02 mol), THF (50 ml), and *n*-butyllithium in hexane (26.6 ml). The resulting dark red solution was stirred at 0° for 0.5 hr, then poured into stirred water (50 ml) to furnish a yellow solution. After neutralization of the latter solution using glacial acetic acid followed by solid sodium bicarbonate, the organic layer was separated and combined with an ether extract (50 ml) of the aqueous layer. Evaporation of the combined organic solutions afforded a sticky yellow material which was collected, washed with ether (20 ml), and dried. The crude imine IIIb (0.56 g, 16%) was crystallized from toluene (charcoal) to give the pure compound (0.35 g, 10%): mp 183–185°; ν_{max} (Nujol) 3450 (NH), 3330 (NH), 1645 (C=O), 1550, 1500, 1450, 1298, 1170, and 780 cm^{-1}.

Anal. Calcd for $C_9H_{11}N_3O$: C, 61.00; H, 6.26; N, 23.72. Found: C, 60.74; H, 6.13; N, 23.77.

Preparation of 1,3-Dilithio Salt VI″.—This was conducted as for the preparation of 1,3-dilithio salt I″ (see above). Addition of the first molecular equivalent of *n*-butyllithium afforded a white suspension which became yellow during addition of the second molecular equivalent.

Addition Reaction of VI″ with Benzaldehyde.—Freshly distilled benzaldehyde (2.23 g, 0.021 mol) was added during 10 min to the dilithioamide suspension prepared from 3-acetamidopyridine (2.72 g, 0.02 mol), THF (100 ml), and *n*-butyllithium in hexane (26.7 ml) to furnish a pale yellow solution. After being stirred at 0° for 0.5 hr, the solution was poured into stirred water (100 ml). The organic layer was separated, combined with an ether extract (50 ml) of the aqueous layer, and evaporated to provide a yellow oil. The latter was crystallized from ethyl acetate (charcoal) to give carbinol–amide VIIa (0.89 g, 18%) as colorless acicular plates, mp 137–139°. Recrystallization from ethyl acetate raised the melting point to 143–143.5°: ν_{max} (Nujol) 3260 (OH), 3160 (NH), 1655 (C=O), 1525, 1475, 1054, 806, 758, and 700 cm^{-1}.

Anal. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.40; H, 5.83; N, 11.56. Found: C, 69.34; H, 5.81; N, 11.50.

Addition Reaction of VI″ with Benzophenone.—A solution of benzophenone (5.46 g, 0.03 mol) in THF (75 ml) was added during 5 min to the dilithioamide suspension prepared from 3-acetoamidopyridine (3.40 g, 0.025 mol), THF (150 ml), and *n*-butyllithium in hexane (36 ml). The resulting clear blue solution was stirred at room temperature for 2 hr and then poured into stirred water (150 ml). Most of the THF was allowed to evaporate, and the resulting mixture, which contained a heavy red oil, was extracted with a 1:1 mixture of ether and ethyl acetate. The dried (Na_2SO_4) extracts were concentrated to produce a yellow solid which, on crystallization from benzene, afforded carbinol–amide VIIb (3.80 g, 48%) as colorless prisms, mp 165–167°. Two recrystallizations from benzene raised the melting point to 167–167.5° cor. The infrared spectrum ($CHCl_3$) showed bands at ν_{max} 3440–3210 (OH and NH), 1670 (C=O), 1600, 1540, 1480, 1450, 1415, 805, and 698 cm^{-1}.

Anal. Calcd for $C_{20}H_{18}N_2O_2$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.21; H, 5.65; N, 8.69.

Dehydration of Carbinol-Amide VIIa with Sulfuric Acid.—The carbinol-amide VIIa (1.0 g) dissolved during *ca.* 2 hr in concentrated sulfuric acid (10 ml) at 0° to give a dark brown solution; the reaction was exothermic initially. When the solution was poured into stirred ice and water (100 ml), a cream precipitate was obtained. The latter (0.12 g), when dry, was fawn colored and its infrared spectrum suggested the presence of cinnamic acid. Basification of the filtrate with aqueous ammonia solution (29.5%) furnished a colloidal solution which, overnight, deposited crude unsaturated VIII as a cream solid (0.58 g, 63%). Crystallization from acetonitrile afforded pure VIII (0.40 g, 43%) as colorless acicular plates: mp 177–178°; ν_{max} (Nujol) 3220 (NH), 1680 (C=O), 1635 (C=C), 1545, 1410, 1333, 1267, 1175, 974, 854, 810, 764, 704, and 680 cm^{-1}.

Anal. Calcd for $C_{14}H_{12}N_2O$: C, 74.99; H, 5.38; N, 12.49. Found: C, 74.81; H, 5.24; N, 12.56.

Unsaturated amide VIII was independently synthesized by adding warm cinnamoyl chloride (1.83 g, 0.011 mol) to a hot solution of 3-aminopyridine (0.94 g, 0.010 mol) and sodium hydroxide (0.44 g, 0.011 mol) in water (15 ml). An exothermic reaction occurred, and a dark yellow tarry precipitate was obtained which solidified when cool. The crude product VIII (0.70 g, 31%) was crytallized from acetonitrile to provide pure VIII (0.34 g, 15%) as colorless acicular plates, mp and mmp 175.5–177°. The infrared spectrum of this compound was identical with that of the dehydration product from VIIa.

Registry No.—*n*-Butyllithium, 109-72-8; IIa, 16054-89-0; IIb, 16054-90-3; IIIa, 16109-47-0; IIIb, 16054-91-4; IV, 16054-92-5; V, 16054-93-6; VIIa, 16054-94-7; VIIb, 16054-95-8; VIII, 16054-96-9.

The N-Hydroxy Protecting Group in Pyridone Syntheses

RICHARD B. GREENWALD[1] AND CHARLES L. ZIRKLE

Smith Kline & French Laboratories, Philadelphia, Pennsylvania 19101

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We wish to report a new route leading to side chain functionalization of 6-methyl-2-pyridone.[2] This method is illustrated by the synthesis of 2-pyridone-6-alanine (IX), and offers the advantage of producing 6-substituted N-hydroxypyridones as intermediates.

Our attention was first directed toward the N-hydroxy group as a protecting function by reports that the N-hydroxy group could be removed by reduction.[3,4] In practice, it was found that the method of Newbold and Spring,[3] which utilizes stannous chloride, gave excellent yields of the desired 2-pyridone derivatives.

The reaction of ethyl oxalate and 4-methyl-2-benzyloxypyridine-1-oxide[5] was carried out using conditions similar to those described for the condensation of ethyl oxalate with 4-picoline 1-oxide.[6] Only a small amount of material was isolated from the reaction, and, although it gave a positive ferric chloride test and its infrared spectrum was in agreement with that of an α-keto ester, the compound did not analyze correctly. This result appeared to be inconsistent with the report of Adams and Miyano[6] that 6- methyl-2-benzyloxypyridine 1-oxide (II) condensed smoothly with ethyl oxalate.

In order to help explain the discrepancy in the two results, the reaction sequence carried out by Adams and Miyano[6] was repeated. Peracetic acid oxidation of 2-benzyloxy-6-methylpyridine (I) did indeed yield a compound which possessed the characteristics claimed for 2-benzyloxy-6-methylpyridine 1-oxide (II), but the infrared spectrum of this compound showed conclusively that it was, in fact, 1-benzyloxy-6-methyl-2-pyridone (III).[7] The thermal rearrangement of alkoxypyridine 1-oxides to 1-alkoxy-2-pyridones is a well-documented reaction[8] and evidently the higher reaction temperatures used during the oxidation caused rearrangement of the pyridine 1-oxide. In fact, peracetic acid oxidation of 4-methyl-2-benzyloxypyridine yielded only 3-methyl-1-benzyloxy-2-pyridone in contrast to *m*-chloroperbenzoic acid oxidation which gave only 4-methyl-2-benzyloxypyridine 1-oxide.[5] Even *m*-chloroperbenzoic acid oxidation of 2-benzyloxy-6-methylpyridine (II) produced the rearranged product III.

Condensation of 6-methyl-1-benzyloxy-2-pyridone (III) with ethyl oxalate proceeded smoothly as reported.[6] All attempts to condense 4-methyl-1-benzyloxy-2-pyridone with ethyl oxalate were, however, unsuccessful. Moreover, no starting material could be recovered from the reaction mixture. The reason for the unusual behavior of the 4-methyl compound is not clear. One explanation might be that there is abstraction of a proton from the benzylic carbon atom leading to benzaldehyde and 4-methyl-2-pyridone (which is water soluble).[9] This process does not appear to be as sterically favorable in the case of the 6-methyl compound III.

The synthesis of the amino acid IX was accomplished as outlined in Scheme I.

Treatment of the α-keto ester IV with hydroxylamine gave the α-oximino ester V already reported by Adams.[5] It seemed advisable to remove the benzyl group from V at this stage in order to prevent possible elimination of benzaldehyde during saponification of the ester. Debenzylation was carried out catalytically[4] and was complete in a few minutes. The product VI gave an intense coloration with aqueous ferric chloride.[3,4] Saponification of VI gave the oximino acid VII which was treated with a solution of stannous chloride in concentrated hydrochloric acid. After the solution had been left standing for several hours at room temperature, the crystalline hydrochloride of the N-hydroxy pyridone amino acid VIII had precipitated. Further treatment of VIII with refluxing stannous chloride–HCl, followed by neutralization, yielded the unsubstituted amino acid IX. Alternatively, treatment of VII with the reduction mixture at reflux gave IX directly. Thus, our original supposition that the N-hydroxy group can be utilized as a protecting group in the syntheses of pyridone derivatives is valid, and appears to offer a method which

(1) Inquiries should be addressed to this author at the Merck Sharpe and Dohme Research Laboratories, Rahway, N. J.

(2) R. L. Gay, S. Boatman, and C. R. Hauser [*Chem. Ind.* (London), 1789 (1965)] have reported a more direct method of obtaining derivatives of 6-methyl-2-pyridone.

(3) G. T. Newbold and F. S. Spring, *J. Chem. Soc.*, 1864 (1948).

(4) E. Shaw, *J. Amer. Chem. Soc.*, **71**, 67 (1949).

(5) W. A. Lott and E. Shaw, *ibid.*, **71**, 70 (1949).

(6) R. Adams and S. Miyano, *ibid.*, **76**, 3168 (1954).

(7) This finding has also been observed independently by E. C. Taylor, Princeton University, private communication, 1966.

(8) F. J. Dinan and H. Tieckelmann, *J. Org. Chem.*, **29**, 1650 (1964).

(9) W. Feely, W. L. Lehn, and V. Boekelheide [*ibid.*, **22**, 1135 (1957)] have prepared benzaldehyde by treating 1-benzyloxypyridinium bromide with alkali.