Nucleophilic Substitutions on the Pyridine Ring with Enolate Anions

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The enolate anions of 5-alkylbarbituric acids and isopropylidene alkylmalonates are demonstrated to readily displace chloro, pyridinio, and acetoxy substituents from the 4-position of simple pyridine derivatives under conditions in which the ring nitrogen carries a positive charge.

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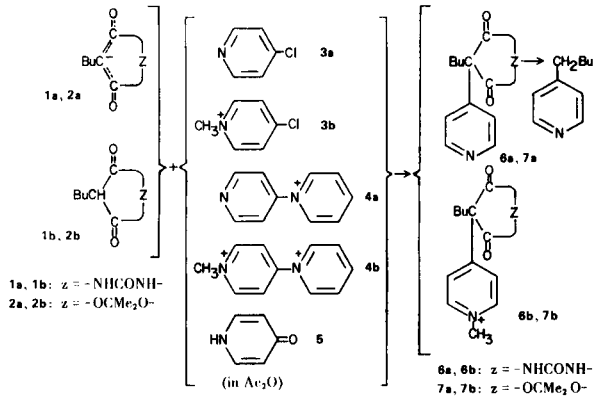
Prior to the recent work of Taylor and Martin (2), general methods for the attachment of carbon-chain substituents to the pyridine ring were almost nonexistent. Electrophilic substitutions of the Friedel-Crafts type are uniformly unsuccessful; nucleophilic substitutions in which a carbon atom is the nucleophilic center have succeeded only sporadically. For example, displacement of halogen from the 4-position by malonic ester anions has been accomplished only when the pyridine ring carried other electron-attracting substituents, as in the 2,6-bis(ethoxycarbonyl) (3), 3-nitro (4), and pentachloro (5) derivatives; we have confirmed the earlier report (3) that the reaction fails with 4-chloropyridine itself.

One apparently general procedure was described many years ago by Gebauer (6): 4-halopyridines or *N*-(4-pyridyl)-pyridinium salts when heated with 5-alkylbarbituric acids yielded 5-alkyl-5-(4-pyridyl)barbituric acids, which were

Scheme I

(Formulas given are those of the starting materials, not necessarily the reacting species)



then hydrolyzed and decarboxylated to 4-alkylpyridines. The objects of the present research were to examine the factors contributing to the success of this process and to explore its range of applicability. We have been chiefly concerned with the reactions shown in Schemes I and II. The separate listing of the enolate anions and their conjugate acids in Scheme I is justified by the difference in their behavior.

Our results can be summarized as follows:

a) The sodium salt of 5-butylbarbituric acid (which contains the ion **1a**) reacts readily with the *N*-methyl-4-chloropyridinium or *N*-(*N'*-methyl-4-pyridinio)pyridinium cation (**3b** or **4b**) to produce **6b**, much more readily than the free acid (**1b**) does.

b) The sodium salt does not react with the unmethylated compounds **3a** or **4a**.

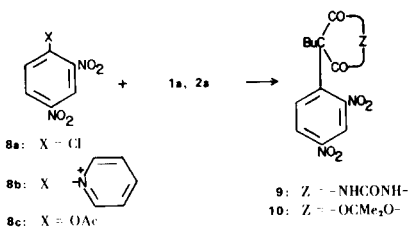
c) The acid **1b** reacts reluctantly with **3a** or **4a** to produce **6a** in moderate yield.

d) Addition of acetic anhydride to the reaction mixture in (c) greatly promotes the reaction. This recalls our previous report (7) that 4-(1*H*)pyridinone (**5**) reacts readily with **1b** in acetic anhydride solution to give **6a**.

e) Isopropylidene butylmalonate (**2b**) and its sodium salt (**2a**-Na^+) behave similarly to **1b** and **1a**, respectively, as far as they have been tested.

We conclude, therefore, that enolate anions can effect nucleophilic displacements at the 4-position of otherwise unsubstituted pyridine *provided the ring nitrogen carries a positive charge* (8). In case (a) above, where these conditions are met, reaction is easy. In case (c) (Gebauer's original conditions), the anion and the positive nitrogen can be generated simultaneously by proton transfer, and reaction is possible but much more difficult. In case (b),

Scheme II



the nitrogen cannot acquire a positive charge and no reaction takes place. On this basis, the failure of 4-chloropyridine to undergo displacement reactions with malonic ester anions may be attributed to the unlikelihood that the nitrogen atom will be protonated under the strongly basic conditions necessary to generate the anion.

Since isopropylidene alkylmalonates and 5-alkylbarbituric acids have about the same acidity, it is reasonable that they should behave similarly in these reactions.

The promoting effect of acetic anhydride may be traced to its known (9) ability to convert pyridine derivatives to some extent into *N*-acetylpyridinium ions, which carry the necessary charge. In particular, 4-(1*H*)pyridinone (**5**) reacts with acetic anhydride to form *N*-acetyl-4-(1*H*)pyridinone, which is in equilibrium with 4-acetoxypyridine in solution (10,11). It is reasonable to suppose that the solution also contains at least a small amount of *N*-acetyl-4-acetoxypyridinium acetate, and that the reactions of **1b** and **2b** with **5** in acetic anhydride solution represent nucleophilic displacements of acetate ion by the ions **1a** and **2a**, the latter being formed by proton transfer to the acetate ion formed in the acetylation of **5**.

When working with 4-halopyridines, one must consider the possibility that polymerization by autoquaternization may precede displacement. Autoquaternization is catalyzed by Lewis acids and inhibited by bases (12); we have similarly observed acceleration of the polymerization of 4-chloropyridine by acetic anhydride. In the resulting polymer, there is a positive charge on every ring nitrogen atom except the terminal one; nucleophilic displacement accompanied by chain rupture should therefore be possible at any ring in the chain. In fact, we have found the thermally-produced polymer of **3a** to react with **1b** under the same conditions and with the production of **6a** in the same yield as when **3a** itself was used. We conclude that autoquaternization may very well take place under acidic conditions but does not substantially affect the ultimate outcome of the reaction; under basic conditions, as when **1a** is heated with **3a**, neither displacement nor autoquaternization is observed.

Reactions involving the 2,4-dinitrophenyl system are of course classical examples of nucleophilic aromatic displacement, and the similarity between pyridinium ions and 2,4-dinitrophenyl derivatives in their behavior toward hydroxide ion has already been pointed out (13). We have extended this similarity by establishing that **1a** and **2a** are capable of displacing chloride ion, pyridine, and acetate ion from the respective 2,4-dinitrophenyl derivatives (Scheme II) under conditions comparable to those used with the 4-substituted pyridinium ions. (We have found no previous instance of the removal of acetate ion from 2,4-dinitrophenyl acetate by displacement at the ring carbon atom.) The pyridinium derivatives are more reactive than the 2,4-dinitrophenyl derivatives, and displacement of chloride ion from either kind of ring is more rapid than displacement of pyridine.

The reaction of **3a** or **4a** with an appropriately substituted barbituric acid or isopropylidene malonate in dimethylformamide-acetic anhydride solution, followed by hydrolysis and decarboxylation of the condensation product (6,7) should be a useful synthetic route towards a variety of 4-alkylpyridines.

EXPERIMENTAL

Proton magnetic resonance spectra were recorded on a Varian A-60A spectrometer and chemical shifts are reported in ppm from TMS unless otherwise noted. Infrared spectra were recorded on a Perkin-Elmer 237B spectrometer as Nujol mulls and are reported in cm^{-1}. Melting points were obtained with an aluminum block apparatus and are uncorrected.

N-Methyl-4-chloropyridinium Chloride (**3b**).

A solution of *N*-methyl-4-chloropyridinium iodide (14) in methanol was passed through a column of Amberlite IRA-400 (Rohm and Haas Co.) and evaporated to give the crude crystalline chloride in quantitative yield. The pure product was obtained as colorless crystals from ethanol-acetone (1:4), m.p. 196-198° dec.; pmr (DMSO-d_6): 4.38 (s, 3H), 8.20-8.54 (m, 2H), 9.04-9.38 (m, 2H).

Anal. Calcd. for $C_6H_7Cl_2N$: C, 43.93; H, 4.30; N, 8.54. Found: C, 43.82; H, 4.39; N, 8.36.

N-(*N'*-Methyl-4-pyridinio)pyridinium Dichloride (**4b**).

The oil obtained by the method of Black and Summers (15) upon heating *N*-(4-pyridyl)pyridinium chloride hydrochloride with dimethyl sulfate was washed twice with a large volume of ether, dissolved in methanol, and passed through a column of Amberlite IRA-400. The eluate was concentrated to an oil and acetone added. Filtration and washing with acetone afforded a nearly quantitative yield of crystalline product, m.p. 225-226° dec. Recrystallization from ethanol gave colorless crystals, m.p. 227-228° dec.; pmr (deuterium oxide, ppm from DOH) -0.11 (s, 3H), 3.5-4.3 (m, 5H), 4.5-4.8 (m, 4H).

Anal. Calcd. for $C_{11}H_{12}Cl_2N_2$: C, 54.34; H, 4.98; N, 11.53. Found: C, 54.08; H, 5.07; N, 11.38.

Isopropylidene Butylmalonate (**2b**).

The literature procedure for the ethyl homolog (16) was followed, substituting butylmalonic acid for ethylmalonic acid, to give a 73% yield of product, m.p. 48-50°. Recrystallization from hexane gave colorless needles, m.p. 57-58°.

Anal. Calcd. for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 59.93; H, 8.06.

The sodium salt (**2a**-Na^+) was prepared by mixing equivalent volumes of sodium ethoxide and the cyclic ester, each one molar in ethanol, and completing the precipitation of the product with ether-hexane (1:1). The white precipitate was filtered out, washed with ether, and vacuum-dried to give an almost quantitative yield of product, dec. >250°.

Anal. Calcd. for $C_{10}H_{15}O_4Na$: Na, 10.4. Found: Na, 10.4.

Sodium 5-Butylbarbiturate (**1a**-Na^+).

A one molar solution of sodium methoxide in methanol was added to twice its volume of a 0.5 molar solution of 5-butylbarbituric acid (**1b**) in methanol. After chilling for 1 hour, the solid precipitate was filtered out, washed thoroughly with methanol, and vacuum-dried. The white powdery product, dec. >350°, was obtained in nearly quantitative yield.

Anal. Calcd. for $C_8H_{11}O_3N_2Na$: Na, 11.2. Found: Na, 10.9.

5-Butyl-5-(4-pyridyl)barbituric acid (**6a**).

A dimethylformamide (DMF) solution of 4-chloropyridine (**3a**) and 5-butylbarbituric acid (**1b**), 1 molal in each reagent, was heated for four hours at 100°; the originally colorless solution became a deep clear red. A thin-layer chromatogram on silica gel with ether as solvent showed almost complete disappearance of **3a**, two spots identified as **1b** and 5-butyl-5-(4-pyridyl)barbituric acid (**6a**), which appeared with about equal intensity, and a large amount of yellow material at the origin. Continued heating produced no further change in the tlc pattern, and aqueous workup after six hours gave a 50% yield of **6a**. The yield obtained from an identical mixture heated at 100° for 24 hours was no better. When the reaction was allowed to proceed at 35°, only a trace of **6a** was obtained from the dark red solution after a few days' time, although 70-80% of the chlorine had by then been liberated as the ion (titration with silver nitrate).

A solution of **1b**, 522 mg. (3 mmoles), and **3a**, 226 mg. (2 mmoles), in 2 ml. of DMF-acetic anhydride (1:1) was kept at 35° for four days. The reaction mixture was treated with dilute hydrochloric acid and filtered to remove unreacted **1b**, and sodium bicarbonate was added to precipitate the product. The white powder was filtered out, washed with water, and dried under vacuum to give 468 mg. (89%) of product, m.p. 250-252° dec. Recrystallization from ethanol gave the pure material, m.p. 256-258° dec., lit. m.p. 260° (6b); pmr (DMSO-d_6): 0.85 (dist. t, 3H), 1.0-1.5 (m, 4H), 2.1-2.4 (m, 2H), 7.2-7.5 (m, 2H), 8.3-8.8 (m, 2H), 11.75 (s, 2H); ir: 1600 (s), 1690 (irreg. vs), 1720 (vs), 1760 (s), 3220 (s).

Anal. Calcd. for $C_{13}H_{15}N_3O_3$: C, 59.76; H, 5.79; N, 16.09. Found: C, 59.65; H, 5.69; N, 16.04.

The reaction of *N*-(4-pyridyl)pyridinium chloride (**4a**) (17) with **1b** in DMF solution, 1 molal in each reactant, at 100° for five hours gave only a 1% yield of **6a**. Under otherwise identical conditions, the use of DMF-acetic anhydride as solvent afforded a 66% yield of the same product.

By contrast, solutions of **3a** and **1a**-Na^+, 1 molal in each reagent, in DMSO-d_6 (examined by pmr) or in DMF (**1a** partially soluble, examined by tlc) showed no reaction of any kind in over three weeks at 35° or on heating at 100° for several days. Mixtures of **4a** and **1a**-Na^+ were equally unreactive.

Isopropylidene Alkyl(4-pyridyl)malonates.

A solution one molal in **3a** and 1.5 molal in the isopropylidene alkylmalonate was prepared in DMF-acetic anhydride (1:1). After standing at room temperature for 4 days, the solution was diluted with crushed ice. Sodium bicarbonate was added to precipitate the product which, after chilling for 1 hour, was filtered out, washed with water, and dried under vacuum.

a) Isopropylidene ethyl(4-pyridyl)malonate, m.p. 128-130°, was obtained from 226 mg. of **3a** and 515 mg. of isopropylidene ethylmalonate in 36% yield. Recrystallization from hexane gave colorless needles, m.p. 133-134°; pmr (deuteriochloroform): 1.0 (t, 3H), 1.4 (s, 3H), 1.7 (s, 3H), 2.3 (q, 2H), A_2B_2 system with doublets at 7.4 and 8.6; ir: 1600 (s), 1735 (vs), 1775 (s).

Anal. Calcd. for $C_{13}H_{15}NO_4$: C, 62.63; H, 6.07; N, 5.62. Found: C, 62.55; H, 5.90; N, 5.51.

b) Isopropylidene butyl(4-pyridyl)malonate (**7a**) was obtained from **3a** and **2b** in 60% yield, m.p. 80-85°. Recrystallization from hexane gave colorless buttons, m.p. 91-92°; pmr (carbon tetrachloride): 1.0 (dist. t, 3H), 1.4 (singlet superimposed on multiplet, 7H), 1.8 (s, 3H), 2.3 (m, 2H), A_2B_2 system with doublets at 7.4 and 8.6; ir: 1600 (s), 1735 (vs), 1775 (s).

Anal. Calcd. for $C_{15}H_{19}NO_4$: C, 64.96; H, 6.91; N, 5.05. Found: C, 65.20; H, 6.63; N, 5.20.

Heating **3a** with **2b** without solvent or in DMF without acetic anhydride resulted in extensive decomposition of **2b** and afforded only a very small yield of **7a**.

N-Methyl-4-[5-(5-butylbarbituryl)]pyridinium Chloride (**6b**).

a) A solution of **3b** and **1a**-Na^+ in dimethyl sulfoxide (DMSO), one molal in each reactant, was prepared. After 1 hour the solution was diluted with ethanol and the precipitated sodium chloride removed by filtration. The clear colorless filtrate was evaporated to an oil, which upon the addition of acetone crystallized to shiny leaflets. These were filtered out, washed with acetone, and dried under vacuum to give a nearly quantitative yield of product, m.p. 242-244° dec. Recrystallization from ethanol by the addition of acetone gave colorless leaflets, m.p. 242-244° dec.; pmr (DMSO-d_6): 0.88 (dist. t, 3H), 1.25 (m, 4H), 2.2-2.6 (signal superimposed on DMSO-d_5), 4.43 (s, 3H), A_2B_2 system with doublets centered at 8.22 and 9.19; ir: 1650 (m), 1680 (m), 1700 (vs), 1725 (s), 1750 (m).

Anal. Calcd. for $C_{14}H_{18}ClN_3O_3$: C, 53.93; H, 5.81; N, 13.48. Found: C, 53.73; H, 5.97; N, 13.03.

When the above reaction was carried out in a pmr tube at 35° with DMSO-d_6 as solvent, the spectral changes showed that the reaction took place as fast as **1a** was added.

b) A DMF suspension one molal in both **4b** and **1a**-Na^+ was prepared and stirred 30 minutes at 100°. The light brown cloudy mixture was diluted with ethanol, filtered, and evaporated to an oil. Addition of acetone caused the separation of crystals, which were filtered out, washed with acetone, and vacuum-dried. The light tan crystals (84% yield) had m.p. 232-237°.

The above compound was identical (ir and pmr) to that obtained by treating **6a** successively with dimethyl sulfate and Amberlite IRA-400.

N-Methyl-4-[5-(5-butyl-2,2-dimethyl-4,6-dioxo-1,3-dioxanyl)]-pyridinium Chloride (**7b**).

A thin ethanol slurry 0.5 molal in both **3b** (82 mg.) and **2a**-Na^+ (111 mg.) was stirred for 30 minutes at room temperature. The light yellow suspension was then diluted with acetone and the precipitated sodium chloride removed by filtration. The filtrate was reduced in volume and chilled. The abundant colorless crystals which separated were filtered out and washed with acetone, m.p. 189-190° dec., (77% yield). Recrystallization from acetone-ether gave hygroscopic colorless crystals, m.p. 188-189° dec., which repeatedly analyzed as a monohydrate after drying under vacuum; pmr (DMSO-d_6): 0.84 (dist. t, 3H), 1.22 (m, 4H), 1.57 (s, 3H),

1.77 (s, 3H), 2.3 (signal superimposed on DMSO-d_5), 4.38 (s, 3H), A_2B_2 system with doublets centered at 8.11 and 9.15; ir (potassium bromide): 1290 (s), 1740 (vs), 1780 (s). Both pmr and ir also indicated the presence of water. As in the case of **3b** and **1a**-Na^+, pmr spectroscopy showed this reaction to take place at 35° as fast as the reagents were mixed.

Anal. Calcd. for $C_{16}H_{22}ClNO_4 \cdot H_2O$: C, 55.57; H, 6.99; N, 4.04. Found: C, 55.89; H, 7.12; N, 3.94.

This compound was identical (ir) to that obtained by treating **7a** successively with dimethyl sulfate and Amberlite IRA-400.

5-Butyl-5-(2,4-dinitrophenyl)barbituric Acid (**9**).

a) A DMSO solution, one molal in both 1-chloro-2,4-dinitrobenzene (**8a**) and **1a**-Na^+, was allowed to stand overnight at 35°. The clear solution was diluted with water, and the precipitate was filtered out, washed with water, and dried under vacuum, to obtain the light yellow product in 89% yield, m.p. 245-250°. The pure product was obtained as faint yellow crystals from ethanol, m.p. 256-258°; pmr (DMSO-d_6): 0.60-1.70 (m, 7H), 2.24-2.70 (signal superimposed on DMSO-d_5), 7.96-8.34 (m, 1H), 8.44-8.82 (m, 2H), 11.74 (s, 2H); ir: 1350 (s), 1530 (s), 1610 (m), 1720 (vs), 1730 (s), 1760 (m).

Anal. Calcd. for $C_{14}H_{14}N_4O_7$: C, 48.00; H, 4.03; N, 16.00. Found: C, 47.94; H, 3.85; N, 15.89.

b) A DMF solution, 0.50 molal in both **1a**-Na^+ and *N*-(2,4-dinitrophenyl)pyridinium chloride (**8b**) (18), was heated at 100° for nine hours. A workup similar to that in paragraph (a) yielded 34% of crude product. If the reaction is allowed to proceed at 35° for several days, a slightly lower yield is obtained.

c) A DMSO solution, 1 molal in both **1a**-Na^+ and 2,4-dinitrophenyl acetate (**8c**), was allowed to stand for four days at room temperature. A 34% yield of **9** was obtained. 2,4-Dinitrophenol was identified as a by-product.

Isopropylidene Butyl(2,4-dinitrophenyl)malonate (**10**).

A DMSO suspension, one molal in both **8a** and **2a**-Na^+, was stirred at 35° overnight. A procedure similar to that above gave an 82% yield of crude product, m.p. 163-165° dec. The pure product was obtained as faint yellow crystals from ethanol, m.p. 176-177° dec.; ir: 1530 (vs), 1610 (s), 1740 (vs), 1780 (s).

Anal. Calcd. for $C_{16}H_{18}N_2O_8$: C, 52.46; H, 4.95; N, 7.65. Found: C, 52.53; H, 4.84; N, 7.58.

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