SYNTHESIS OF NOVEL AZAPYRIDOCYANINES

Shekhar Munavalli, Fu-Lian Hsu, and Edward J. Poziomek

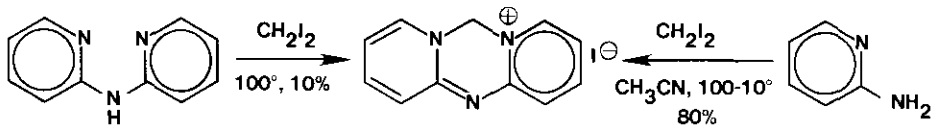
U.S. Army Chemical Research, Development and Engineering Center
Research Directorate
Aberdeen Proving Ground, MD 21010-5423, U.S.A.

Abstract - A facile synthesis of azapyridocyanines from substituted 2-aminopyridines and dihalomethane is described. The influence of the substituents on the course of the reaction and the scope of the synthesis have been further explored.

The suggestion[1,2] that the coupling of the azapyridocyanine moiety to a conjugated polymeric backbone might yield superconducting polymers has generated considerable interest[3-6] in the synthesis of this novel group of heterocycles. There are no effective condensation procedures available for the preparation of these heterocyclic compounds[2]. Difficulties are usually encountered in their routine preparation[7]. The only reported synthesis was accomplished through quaternization of 2,2'-dipyridylamine with appropriate alkyl dihalides[2]. However, the quaternization of 2,2'-dipyridylamine suffers from a severe steric hindrance from the bulky substituent, namely the 2-pyridylamino group[8]. The overall contribution of the steric factor is reflected in the poor yield of the parent compound and the problems associated with the isolation of the product[2].

Recently we reported[3] an efficient synthesis of N,N'-methylene-2,2'-azapyridocyanine (1) from 2-aminopyridine and methylene iodide and its structure determination by X-ray crystallography has been accomplished[6]. In addition, the isolation and purification of the expected products were straightforward and did not entail any elaborate procedures. With a view to explore the general applicability, the scope and the limitation of this condensation reaction, we have now completed a comprehensive study of the facile one-step synthesis of the azapyridocyanines.

The condensation procedure involves the initial formation of the methylene bridge between two pyridine nitrogens. This bisquaternization, as is to be expected, is highly sensitive to the electronic environment of the aminopyridines. Any substituent that alters the electron density of the ring nitrogen and that reduces the nucleophilicity of the exocyclic amino function affects the course of the reaction. Thus, electron donating groups facilitate the reaction. On the other hand, the presence of electron withdrawing groups on the pyridine ring results in the failure of the reaction.



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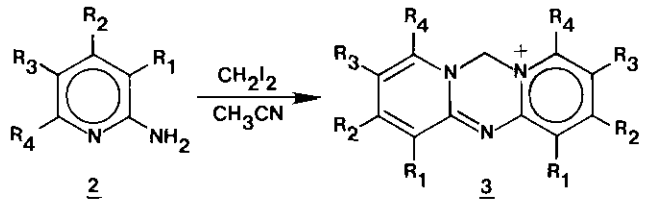
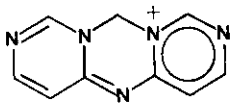


2 3

2a, $R_1 = CH_3$, $R_2 = R_3 = R_4 = H$
2b, $R_2 = CH_3$, $R_1 = R_3 = R_4 = H$
2c, $R_3 = CH_3$, $R_1 = R_2 = R_4 = H$
2d, $R_4 = CH_3$, $R_1 = R_2 = R_3 = H$

3a, $R_1 = CH_3$, $R_2 = R_3 = R_4 = H$
3b, $R_2 = CH_3$, $R_1 = R_3 = R_4 = H$
3c, $R_3 = CH_3$, $R_1 = R_2 = R_4 = H$



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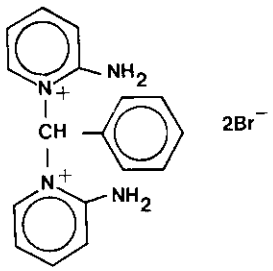

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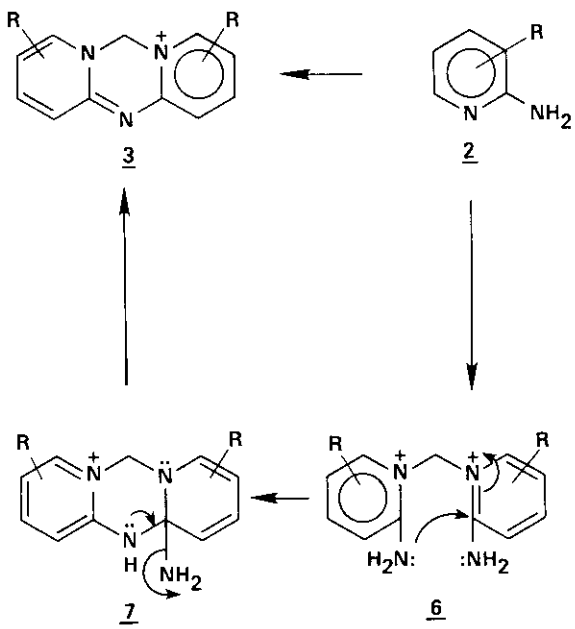

R = CH_3

SCHEME 1

Thus, 2-aminopicolines (2a-2c) reacted very smoothly with methylene iodide to give 3a-3c in acceptable yields. The reaction of nitro- or bromo-substituted 2-aminopyridine; such as 2-amino-3-nitropyridine, 2-amino-5-nitropyridine, 2-amino-5-bromopyridine and 2-amino-3,5-dibromopyridine; failed to yield the desired product even at 160° C in a pressure bottle. We have also examined the reaction of aminopyrimidines and aminopyrazine. Of the three starting materials (2-aminopyrimidine, 4-aminopyrimidine and aminopyrazine) only 4-aminopyrimidine gave the expected product, 4 . The reaction of 2-amino-substituted five membered diheterocyclic compounds and di-iodomethane also failed. The only compounds we were able to isolate and identify were the starting materials themselves.

The condensation procedures appears to be highly susceptible to the influence of the steric factors. This was demonstrated by the failure to obtain the expected tricyclic product from the reaction of 2-amino-6-picoline with methylene iodide. In the case of 2-amino-6-picoline, the ring nitrogen atom is flanked by two bulky groups, namely the methyl and amino substituents. This causes considerable steric hindrance and obstructs the primary process of bisalkylation of the pyridine nitrogen, a step necessary prior to the closure of the ring. That bisquaternization of the pyridine nitrogen is a pre-requisite for the formation of this novel group of tricyclic azapyridocyanine derivatives has been demonstrated by the isolation and characterization on N,N'-phenylmethylene-2,2'-diaminobispyridinium iodide (5)[9]. The steric hindrance present in 2-amino-6-picoline (2d) profoundly alters the normal course of the reaction and results in an unusual nitrogen to carbon double migration[10]. Thus, the formation of 3 from 2-aminopicolines must have involved the initial bisquaternization of the pyridine nitrogen to give intermediate of the type (6), followed by the ring closure (7) and the subsequent elimination of ammonia (cf. Scheme 1).

EXPERIMENTAL

All melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The infrared spectra of the solid samples were obtained as potassium bromide disks on a Perkin-Elmer Model 1420 Spectrophotometer. The NMR spectra were obtained on a Varian-EM390 NMR spectrophotometer in D_2O using sodium 3-trimethylsilylpropionate (TSP) as an internal standard (δ = 0.00). The UV spectra were recorded on a Cary 17D recording spectrophotometer. The elemental analysis were obtained through the Analytical Division, Chemical Research, Development and Engineering Center.

N,N'-Methylene-3,3'-dimethyl-2,2'-azapyridocyanine (3a).

A solution of 2-amino-3-picoline (2a) (1.08 g, 0.01 mole) and methylene iodide (2.68 g, 0.01 mole) in 25 ml of dry acetonitrile was refluxed for 48 h. The solvent was evaporated under reduced pressure and the resulting viscous residue was dissolved in ethanol and the crude product was

precipitated by the addition of dry ether. The compound was recrystallized from ethanol/ether to give 0.341 g (34%) of bright yellow crystals of 3a, mp 214-216°C; ^{1}H-NMR: δ 2.50 (s, 6H, $2CH_3$), 6.34 (s,2H,N-CH_2-N), 7.19 (t, 2H, ArH, J= 6.0 Hz), 7.93 (t,4H, ArH, J=6.0 Hz). UV (H_2O, nm): 406, 316, 273, 223(sh)205; log ε 4.318, 3.702, 3.887, 4.285, 4.429. Anal. Calc. for $C_{13}H_{14}N_3I$: C, 46.03; H, 4.16; N, 12.39. Found: C,45.85; H, 4.05; N, 12.28.

N,N'-Methylene-4,4'-dimethyl-2,2'-azapyridocyanine (3b).

A mixture of 2-amino-4-picoline (2b) (1.08 g, 0.01 mole) and methylene iodide (2.68 g, 0.01 mole) in 25 ml of dry acetonitrile was reflused for 48 h. The solvent was removed under reduced pressure, the residue was washed with ether and then triturated with ethanol to give 0.41 g (42%) of a golden yellow solid. The analytical sample was recrystallized from ethanol/ehter: yellow crystals, mp 236-238°C; ^{1}H-NMR: δ 2.45 (s, 6H, $2CH_3$), 6.18 (s, 2H, CH_2), 7.01 (d, 2H, ArH, J = 2.0 Hz), 7.05 (dd, 2H, ArH, J=2.0, 7.0 Hz), 7.80 (d, 2H, ArH, J=7.0 Hz). UV (H_2O, nm): 388, 305, 275; log ε 4.431, 3.854, 4.082. Anal.Calc. $C_{13}H_{14}N_3I$: C, 46.03; H, 4.16; N, 12.39. Found: C, 45.81; H, 4.24; N, 12.09.

N,N'-Methylene-5,5'-dimethyl-2,2'-azapyridocyanine (3c).

A solution of 2-amino-5-picoline (1.08 g, 0.01 mole) and methylene iodide (2.68 g, 0.01 mole) in 30 ml of dry acetonitrile was refluxed for 48 h. The yellow precipitate was filtered and washed with acetone to furnish 0.425 g of 3c. The filtrate yielded another 0.1 g. The combined product (0.525 g, 53%) was recrystallized from ehanol/ether to afford golden yellow colored crystals, 3c, mp 256-258°C; ^{1}H-NMR: δ 2.30 (s, 6H, $2CH_3$), 6.30 (s, 2H, CH_2), 7.12 (d, 2H, ArH, J=9.0 Hz), 7.74 (d, 2H, ArH, J=2.7 Hz), 7.89 (dd, 2H, ArH, J=2.7, 9.0 Hz). UV (H_2O, nm): 406, 310, 265, 208; log ε 4.204, 3.670, 4.020, 4.531. Anal. Calc. for $C_{13}H_{14}N_3I$: C, 46.03; H, 4.16; N, 12.39, I, 37.40. Found: C, 46.12; H, 4.13; N, 12.29, I, 37.12.

N,N'-Methylene-5,5-diaza-2,2'-azapyridocyanine (4).

A mixture of 4-aminopyrimidine (0.48 g, 0.005 mole) and di-iodomethane (1.34g, 0.005 mole) in 25 ml of dry acetonitrile was refluxed for 2 days. On cooling, a sold material precipitated. The solid was filtered and wash successively with ether and acetone to give 0.45 g (57%) of the copper-red colored compound, mp 254-256°C (decomp.). Recrystallation from EtOH-H_2O raised the mp to 273-277°C (decomp.). ^{1}H-NMR: δ 6.25 (s, 2H, CH_2); 6.8 (d, 2H, ArH, J = 8.5 Hz), 8.2 (dd, 2H, ArH, J = 8.5, 2.0 Hz), 8.8 (d, 2H, ArH, J = 2.0 Hz). UV (H_2O, nm): 255, 222; log ε , 4.239, 4.297. Anal. Calc. for $C_9H_8N_5I$: C, 34.52; H, 2.57; N, 22.36. Found: 34.38; H, 2.48; N, 22.26.

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