Hydroxide-Catalyzed Synthesis of Heterocyclic Aromatic Amine Derivatives from Nitriles

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A generalized method for synthesizing a wide variety of heterocyclic aromatic amine derivatives from nitriles by use of hydroxide catalysts is presented. Nitrile dimers (3-aminocrotononitrile and dicyandiamide) and a dimer analog (anthranilonitrile) react with monomeric nitriles in the presence of hydroxide to form respectively, aminopyrimidines, diaminotriazines and aminoquinazolines.

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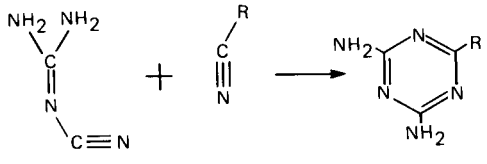
In the past work, nitriles have been condensed to form cyclic trimers (aminopyrimidines or *s*-triazines) under various conditions which include either acid or base catalysts (1,2), high-pressures, and high temperatures (3). Dimers have also been obtained by base-catalyzed condensation of nitriles containing an alpha hydrogen (Thorpe Reaction) (2,4).

The formation of cyclic trimers from the monomeric species involves first the formation of a dimer intermediate which then reacts to yield the trimer. The present work, which concentrates on the second stage of this reaction, describes a generalized reaction scheme for initiating reactions at the dimer stage using mild reaction conditions. The reaction scheme in the present work involves the formation of mixed cyclic trimers by reaction of nitrile dimers (or dimer analogs) with nitrile monomers as given by Reactions 1-3. The respective principle products of these reactions are 6-substituted-2,4-diamino-*s*-triazines, 2-substituted-4-amino-6-methylpyrimidines, and 2-substituted-4-aminoquinazolines. Reaction 1, which involves the cyclic polymerization of dicyandiamide (the dimer of cyanamide) with any monomeric nitrile, has been studied exentsively in past work (5) using a wide variety of basic catalysts including hydroxides. Reaction 2 has not been studied as an independent reaction; however, both the reaction of the monomer to yield dimer and the reaction of monomer to yield trimer have been studied (2) and are directly related to Reaction 2. Reaction 3 has been



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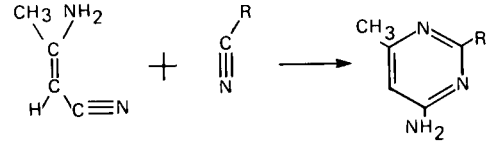

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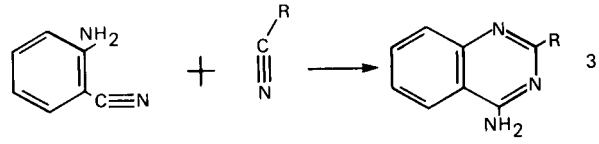

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performed previously using strong bases such as phenyl lithium and sodium methoxide (6) which are inherently less convenient to use than hydroxides. Hydroxide catalysts have been employed for other special-case polymerizations which utilized the nitriles, acrylonitrile (7), glyconitrile (8), and malononitrile (9); however, only the glyconitrile reaction yielded a cyclic polymerization product.

Results and Discussion.

A list of heterocyclic aromatic amine derivatives, which are successfully prepared by the outlined reaction scheme involving the condensation of two nitrile dimers and a dimer analog (anthranilonitrile) with four nitrile monomers is given in Table I. Although Reaction 2 was demonstrated only for the acetonitrile dimer (3-aminocrotonitrile) (10) yielding the 2-substituted-4-amino-6-methylpyrimidines, the reaction may occur with other dimers derived from nitriles containing an alpha hydrogen. The products were obtained in high yields using simple reaction conditions. The yields reported in Table I are based on simple recovery techniques and likely would have been higher if more advanced techniques had been utilized. The efficiency of the reaction is believed to exceed 80% in all cases. The process consisted of heating the appropriate, dried reactants and catalyst mixture in a sealed vial for a short period (usually overnight), then filtering a precipitated, high-purity product upon cooling. The use of strong bases such as sodium metal, sodium hydride, or sodium methoxide was unnecessary since hydroxides were determined to be effective catalysts for promoting the dimer-monomer reaction (Reactions 1-3). The base systems which were utilized included tetramethylammonium hydroxide and ethanolic potassium hydroxide. The use of tetramethylammonium hydroxide was advantageous in the case of a nearly pure nitrile solvent system where potassium hydroxide has low solubility. For Reaction 1;

Table I
Heterocyclic Aromatic Amine Derivatives Synthesized from Nitriles
by Hydroxide-Catalyzed Condensation

Product	Product Yield %	Mp °C	Mp (Literature) °C
4-amino-2,6-dimethylpyrimidine	95	268	263 (5b), 274-275 (5d)
4-amino-2-ethyl-6-methylpyrimidine	94	299	275-276 (11)
4-amino-6-methyl-2-phenylpyrimidine	88	225	222 (5b), 229-231 (12)
4-amino-2-(4-chlorophenyl)-6-methylpyrimidine	86	246-248	251 (5c)
2,4-diamino-6-methyl-*s*-triazine	85	184	184 (13)
2,4-diamino-6-ethyl-*s*-triazine	52	172	169-172 (14)
2,4-diamino-6-phenyl-*s*-triazine	72	131	---
6-(4-chlorophenyl)-2,4-diamino-*s*-triazine	--	129-131	---
4-amino-2-methylquinazoline	42	225	234-235 (15)
4-amino-2-ethylquinazoline	34	225	---
4-amino-2-phenylquinazoline	59	146	143-145 (16)
4-amino-2-(4-chlorophenyl)quinazoline	--	148	---

however, the use of a protic solvent such as ethanol, which was needed to dissolve the dimer reactant dicyandiamide, permitted the use of potassium hydroxide base. Another factor that was considered in the choice of the particular hydroxide catalyst was the solubility of the expected product in the solvent system which was utilized.

In the course of this work it was determined that tetramethylammonium hydroxide, which was utilized in the form of the pentahydrate, was an excellent catalyst for the hydrolysis of nitriles to the corresponding amides. In order to suppress amide formation which was competitive with the nitrile dimer-monomer reaction, all components of a given reaction mixture were dried with Linde 4A Molecular Sieves prior to heating.

The mechanism and kinetics of the dicyandiamide-benzonitrile reaction have been studied by Ogata, *et al.* (12). The reaction mechanism presented in that work appears to successfully explain the series of dimer-monomer reactions in the present work.

Upon prolonged heating, tetramethylammonium hydroxide was found in the present work to convert the nitrile monomer (acetonitrile) having an alpha hydrogen to the cyclic trimer in low yield. Although this is a potential side reaction, no interferences were observed with the reaction described in this report. The lack of observable interferences is due to a large extent to the fact that the rate of conversion of the nitrile monomer to the dimer is much slower than the conversion of the dimer to the cyclic trimer.

Another potential side reaction is the reaction of two nitrile dimer molecules having an alpha hydrogen to yield a six-membered-ring cyclic tetramer. Blanks of dimers run in ethanol with base indicated that a negligible quantitiy of tetramer would be formed under the reaction conditions used in the present work.

EXPERIMENTAL

All melting points were obtained with a Büchi melting point aparatus and are uncorrected. Proton magnetic resonance spectra were recorded on a Bruker 90 MHz HFX nmr spectrometer. Infrared spectra were scanned on a Digilab FTS-15B Fourier transform infrared (FTIR) spectrometer. Combustion analyses were performed on a Perkin-Elmer 240 B elemental analyzer. Product yields and melting point data are presented in Table I

Preparation of 2-Substituted-4-amino-6-methylpyrimidines.

Samples containing ~0.2 g of tetramethylammonium hydroxide pentahydrate and 2.5 g of 3-aminocrotononitrile were mixed separately with ~7.5 g of acetonitrile, propionitrile and benzonitrile. A blank having the same composition, except for substitution of ethanol for the nitrile monomer, was also prepared. *p*-Chlorobenzonitrile was also utilized as a nitrile monomer but was treated differently because it is a solid. In this case, ~2 g of 3-aminocrotononitrile and ~4 g of *p*-chlorobenzonitrile were mixed with ~-6.0 g of ethanol saturated with potassium hydroxide. These solutions were heated in 25-ml glass vials for 15.5 hours at 80°. After refrigeration, solid products were collected from each of the solutions by filtration. The products were then vacuum dried, weighed, and identified by proton nmr and FTIR, as 4-amino-2,6-dimethylpyrimidine, and 4-amino-2-ethyl-6-methylpyrimidine, 4-amino-6-methyl-2-phenylpyrimidine and 4-amino-2-(4-chlorophenyl)-6-methylpyrimidine. The propionitrile and benzonitrile products were found to contain, respectively, major co-precipitated quantities of propionamide and benzamide formed from hydrolysis of the corresponding nitrile monomer. Apparently, in the case of acetonitrile the high solubility of acetamide precluded this amide from being co-precipitated with the pyrimidine product. The experiments with propionitrile and benzonitrile were repeated as previously described with the addition of a predrying step for the monomeric nitrile/tetramethylammonium hydroxide pentahydrate mixtures with Linde 4A Molecular Sieves for 20 hours to suppress amide formation. Analysis of the blank indicated no evidence for the self-polymerization from 3-aminocrotononitrile. Small quantities of the products were recrystallized from acetonitrile and ethanol for melting point determinations and combustion analyses.

Preparation of 6-Substituted-2,4-diamino-*s*-triazines.

Solutions containing ~1 ml of ethanolic potassium hydroxide (saturated), ~0.5 g of dicyandiamide, and ~11 g of ethanol were prepared and mixed separately with ~2.5 g of acetonitrile, propionitrile, benzo-

nitrile and *p*-chlorobenzonitrile. Each reactant was dried over Linde 4A Molecular Sieves prior to reaction to prevent amide formation. A blank having the same composition, except for deletion of the nitrile monomer, was also prepared. These solutions were heated in 25-ml glass vials for 24 hours at 80°. Each of the solutions with the exception of the blank contained a precipitate prior to removal from the oven. After refrigeration these solids were collected by filtration and subsequently vacuum dried and weighed. These solids from the solutions were identified by proton nmr and FTIR as 2,4-diamino-6-methyl-*s*-triazine, 2,4-diamino-6-ethyl-*s*-triazine, 2,4-diamino-6-phenyl-*s*-triazine and 6-(4-chlorophenyl)-2,4-diamino-*2*-triazine. Analysis of the blank indicated no evidence for the self-polymerization of the dicyandiamide.

Preparaton of 2-Substituted-4-aminoquinazolines.

Solutions containing ~1 ml of ethanolic potassium hydroxide (saturated), ~2.5 g of anthranilonitrile, and ~4.5 g of ethanol were mixed separately with ~4.5 g of acetonitrile, propionitrile, and benzonitrile. Each reactant was dried over Linde 4A Molecular Sieves prior to reaction. Another vial contained ~3.5 g of anthranilonitrile, ~4.5 g *p*-chlorobenzonitrile and ~8.0 g of ethanol saturated with potassium hydroxide. These solutions were heated in 25-ml glass vials at 120° for 44 hours. After refrigeration, solid products precipitated from the solutions containing acetonitrile, propionitrile, and *p*-chlorobenzonitrile. For the benzonitrile solution, it was necessary to seed the mixture in order to initiate precipitation. These solids were vacuum dried, weighed and identified by proton nmr and FTIR as 4-amino-2-methylquinazoline, 4-amino-2-ethylquinazoline, 4-amino-2-phenylquinazoline, and 4-amino-2-(4-chlorophenyl)quinazoline. Analysis of a blank solution (no nitrile monomer) indicated no polymerization of the anthranilonitrile. Small quantities of the products were recrystallized from ethanol for melting point determinations and combustion analyses.

Preparation of Cyclic Trimers (Substituted-4-aminopyrimidines) from Monomers.

Hydroxide bases were also found to be partially effective in converting monomers containing an alpha hydrogen to cyclic trimers (substituted-4-aminopyrimidines). A solution containing ~0.6 g of tetramethylammonium hydroxide pentahydrate and ~11 g of acetonitrile was heated for 24 hours at 120°. No effort was made in this experiment to pre-dry any of the reaction components. After refrigeration a precipitate identified as 4-amino-2,6-dimethylpyrimidine in yield of 12% was formed. The solution was also examined and found to contain an appreciable quantity of acetamide (>10%). For a similar reaction using propionitrile instead of acetonitrile, the cyclic trimer of propionitrile (4-amino-2,6-diethyl-5-methylpyrimidine) was observed in lower yield (<5%).

4-Amino-2,6-dimethylpyrimidine.

This compound had: nmr (DMSO-d_6): δ 2.14 (singlet, 3H), 2.28 (singlet, 3H), 6.09 (singlet, 1H), 6.63 (broad singlet, 2H); ir (potassium bromide): ν major 3320, 3132, 1659, 1596, 1544, 1485, 1444, 1417, 1397, 1368, 1190, 985, 838 cm^{-1}.

Anal. Calcd. for $C_6H_9N_3$: C, 58.51; H, 7.37; N, 34.12. Found: C, 58.88; H, 7.42; N, 34.32.

4-Amino-2-ethyl-6-methylpyrimidine.

This compound had: nmr (DMSO-d_6): δ 1.17 (triplet, J = 7 Hz, 3H), 2.14 (singlet, 3H), 2.52 (quartet, 2H), 6.07 (singlet, 1H), 6.56 (broad singlet, 2H); ir (potassium bromide): ν major 3300, 3116, 2969, 1663, 1599, 1550, 1486, 1465, 1420, 1396, 1362, 1190, 976 cm^{-1}.

Anal. Calcd. for $C_7H_{11}N_3$: C, 61.29; H, 8.08; N, 30.63. Found: C, 61.69; H, 8.22; N, 30.89.

4-Amino-6-methyl-2-phenylpyrimidine.

This compound had: nmr (DMSO-d_6): δ 2.26 (singlet, 3H), 6.22 (singlet, 1H), 6.77 (broad singlet, 2H), 7.43 (multiplet, 3H), 8.30 (multiplet, 2H); ir (potassium bromide): ν major 3377, 3329, 3200, 1637, 1596, 1582, 1542, 1473, 1450, 1410, 1381, 861, 802 cm^{-1}.

Anal. Calcd. for $C_{11}H_{11}N_3$: C, 71.33; H, 5.99; N, 22.68. Found: C, 71.64; H, 6.00; N, 22.76.

4-Amino-2-(4-chlorophenyl)-6-methylpyrimidine.

This compound had: nmr (DMSO-d_6): δ 2.28 (singlet, 3H), 6.22 (singlet, 1H), 6.78 (broad singlet, 2H), 7.50 (doublet, J = 7 Hz, 2H), 8.28 (doublet, J = 7 Hz, 2H); ir (potassium bromide): ν major 3491, 3389, 3310, 3192, 1638, 1599, 1572, 1543, 1495, 1466, 1433, 1393, 1377, 1195, 1092, 1013, 833, 783 cm^{-1}.

Anal. Calcd. for $C_{11}H_{10}ClN_3$: C, 60.14; H, 4.59; N, 19.13. Found: C, 59.62; H, 4.54; N, 18.76.

2,4-Diamino-6-methyl-*s*-triazine.

This compound had: nmr (DMSO-d_6): δ 2.06 (singlet, 3H), 6.61 (broad singlet, 4H); ir (potassium bromide): ν major 3511, 3386, 3307, 3125, 1658, 1627, 1550, 1459, 1420, 1274, 1017, 819, 573, 563, 535 cm^{-1}.

Anal. Calcd. for $C_4H_7N_5$: C, 38.39; H, 5.64; N, 59.97. Found: C, 38.26; H, 5.59; N, 56.36.

2,4-Diamino-6-ethyl-*s*-triazine.

This compound had: nmr (DMSO-d_6): δ 1.13 (triplet, J = 7 Hz, 3H), 2.33 (quartet, 2H), 6.60 (broad singlet, 4H); ir (potassium bromide): ν major 3330, 3157, 2980, 1673, 1642, 1537, 1461, 1407, 1312, 1237, 1022, 830, 605 cm^{-1}.

Anal. Calcd. for $C_5H_9N_5$: C, 43.15; H, 6.52; N, 50.33. Found: C, 43.22; H, 6.55; N, 50.72.

2,4-Diamino-6-phenyl-*s*-triazine.

This compound had: nmr (DMSO-d_6): δ 6.73 (broad singlet, 4H), 7.44 (multiplet, 3H), 8.22 (multiplet, 2H); ir (potassium bromide): ν major 3454, 3399, 3303, 3185, 1622, 1594, 1543, 1495, 1455, 1430, 1263, 831, 784, 703 cm^{-1}.

Anal. Calcd. for $C_9H_9N_5$: C, 57.74; H, 4.85; N, 37.41. Found: C, 57.71; H, 4.82; N, 37.41.

6-(4-Chlorophenyl)-2,4-diamino-*s*-triazine.

This compound had: nmr (DMSO-d_6): δ 6.86 (broad singlet, 4H), 7.53 (doublet, J = 7 Hz, 2H), 8.30 (doublet, J = 7 Hz, 2H); ir (potassium bromide): ν major 3501, 3393, 3319, 3195, 1651, 1628, 1591, 1545, 1437, 1396, 1086, 810, 743, 411 cm^{-1}.

Anal. Calcd. for $C_9H_8ClN_5$: C, 48.77; H, 3.64; N, 31.60. Found: C, 48.79; H, 3.59; N, 31.40.

4-Amino-2-methylquinazoline.

This compound had: (DMSO-d_6): δ 2.41 (singlet, 3H), 7.3-7.8 (multiplet, 5H), 8.18 (doublet, J = 7 Hz, 1H); ir (potassium bromide): ν major 3320, 3059, 1683, 1653, 1617, 1574, 1553, 1505, 1477, 1394, 1367, 765, 756 cm^{-1}.

Anal. Calcd. for $C_9H_9N_3$: C, 67.90; H, 5.70; N, 26.40. Found: C, 68.30; H, 5.67; N, 26.28.

2-Amino-2-ethylquinazoline.

This compound had: nmr (DMSO-d_6): δ 1.24 (triplet, J = 7 Hz, 3H), 2.67 (quartet, 2H), 7.3-7.8 (multiplet, 5H), 8.14 (doublet, J = 7 Hz, 1H); ir (potassium bromide): ν major 3268, 3227, 3075, 2978, 1684, 1623, 1580, 1564, 1512, 1478, 1397, 1376, 1308, 774 cm^{-1}.

Anal. Calcd. for $C_{10}H_{11}N_3$: C, 69.34; H, 6.40; N, 24.26. Found: C, 69.44; H, 6.37; N, 24.30.

4-Amino-2-phenylquinazoline.

This compound had: nmr (DMSO-d_6): δ 7.4-7.9 (multiplet, 8H), 8.24 (doublet, J = 7 Hz, 1H), 8.3-8.6 (multiplet, 2H); ir (potassium bromide): ν major 3327, 3181, 1644, 1618, 1571, 1547, 1505, 1458, 1441, 1381, 1362, 768, 717 cm^{-1}.

Anal. Calcd. for $C_{14}H_{11}N_3$: C, 76.00; H, 5.01; N, 18.99. Found: C, 76.01; H, 4.93; N, 19.18.

4-Amino-2-(4-chlorophenyl)quinazoline.

This compound had: nmr (DMSO-d_6): δ 7.5-7.9 (multiplet, 7H), 8.28 (doublet, J = 7 Hz, 1H), 8.48 (doublet, J = 7 Hz, 2H); ir (potassium bromide): ν major 3400, 3302, 3180, 1641, 1590, 1572, 1543, 1502, 1454, 1402, 1381, 1356, 1329, 1011, 933, 841, 758 cm^{-1}.

Anal. Calcd. for $C_{14}H_{10}ClN_3$: C, 65.76; H, 3.94; N, 16.43. Found: C, 65.67; H, 4.03; N, 16.39.

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