Lewis Acid Assisted Cyclization of Arylcyanoguanidines to 2,4-Diaminoquinazolines

Michael L. Jones*, Lee F. Kuyper, and Virgil L. Styles

Division of Organic Chemistry,
Burroughs Wellcome Co.,
3030 Cornwallis Road,
Research Triangle Park, NC 27709

J. Marc Caddell

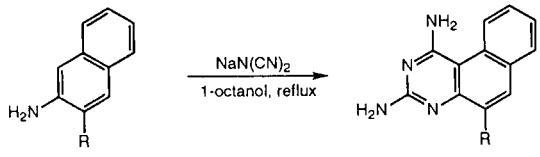
Chemical Development Laboratories,
Burroughs Wellcome Co.,
3030 Cornwallis Road,
Research Triangle Park, NC 27709

Received March 2, 1994

The mild preparation of *N*-cyano-*N'*-(1-*H*-indol-5-yl)guanidine and its cyclization to 1,3-diamino-7*H*-pyrrolo[3,2-*f*]quinazoline is described. Whereas previously reported methods of cyclization employed high temperatures to effect ring closure, we found that certain Lewis acids, such as boron trifluoride etherate, induce cyclization at moderate temperatures.

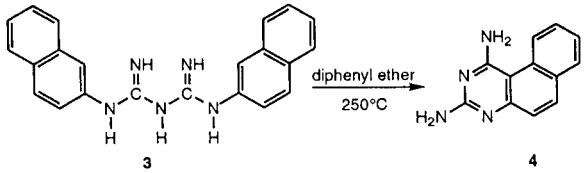
J. Heterocyclic Chem., **31**, 1681 (1994).

The 2,4-diaminoquinazolines are of considerable interest because of their biological properties [1]. Some of the early synthetic work on the quinazoline ring system demonstrated that aminonaphthalenes **1** could be condensed with dicyanamide in refluxing 1-octanol (18-36 hours to provide 2,4-diaminoquinazolines **2** in 8-40% yield [2].



1 2

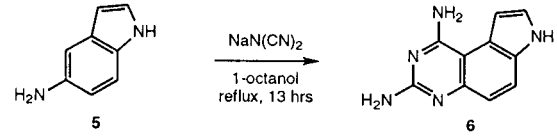
In related work, intermediate **3** was formed from the reaction of two moles of 2-naphthylamine and one mole of dicyanamide in refluxing 2-methoxyethanol in 60-70% yield. The bis(2-naphthyl)biguanidine **3** intermediate was cyclized in diphenyl ether at 250° to give the diaminoquinazoline **4** in 25-40% yield [2c].



3 4

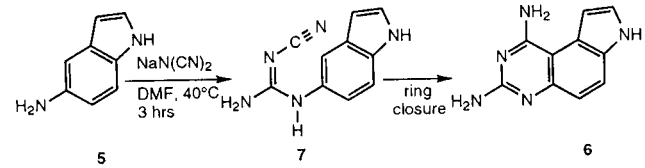
The patent literature [3] provided an analogous condensation of 5-aminoindole **5** and dicyanamide that produced the pyrroloquinazoline **6**.

In our laboratory, this reaction required prolonged heating and was accompanied by considerable decomposition. Typical yields were approximately 40%, and extensive chromatography was necessary.



5 6

In an effort to improve the synthesis of **6**, we isolated a novel intermediate **7** in 90% yield from the reaction of aminoindole **5** with excess (3 equivalents) sodium dicyanamide in dimethylformamide. This result contrasts with the report of Rosowsky and Modest [2c], who isolated the bis adduct **3**. We found that our two-step procedure, utilizing **7** as an isolated intermediate, provided higher overall yields of **6** than attempting a one-pot procedure [3]. Interestingly, both intermediates **3** and **7** cyclize to produce 2,4-diaminoquinazolines.



5 7 6

Utilizing **7** as a starting material, we investigated a variety of thermal conditions to effect ring closure. Refluxing diglyme was particularly convenient for larger scale (2-100 g) preparations, and methanol at 150° in a closed vessel was advantageous for cyclization of smaller amounts of material. The thermal cyclization was also performed in dimethyl sulfoxide and 2-ethoxyethanol, which gave similar results.

The cyclization in refluxing diglyme was studied in some detail, and a typical reaction for which we monitored product formation by hplc is shown in Figure 1. Optimal product formation required 11 hours of heating and, in this instance, the yield was only 30%. However,

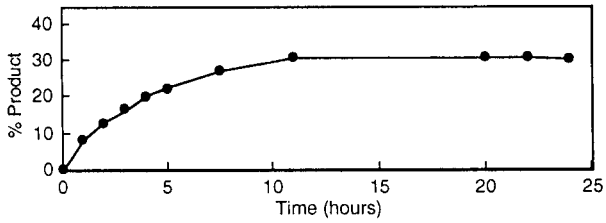
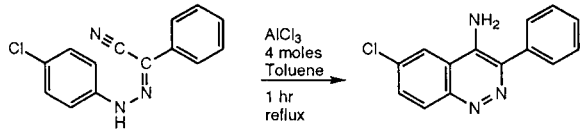


Figure 1. The formation of **6** from **7** in refluxing diglyme (162°) as a function of time. The concentration of **6** was monitored by hplc.

the yields from thermal cyclizations were variable, usually 30-50% and occasionally as high as 58%. Significant decomposition occurred under all thermal conditions, and these results prompted us to search for milder cyclization methods, such as Lewis-acid catalysis.



8 **9**

Although no examples of Lewis acid catalyzed arylcyanoguanidine cyclizations have been reported, analogous intramolecular ring closures involving bond formation between an aromatic ring and a nitrile function are known. For example, Lamant showed that ring closure of **8** to form **9** could be effected using aluminum chloride [4]. Others have used titanium tetrachloride [5] and sulfuric acid [6] to promote similar cyclizations.

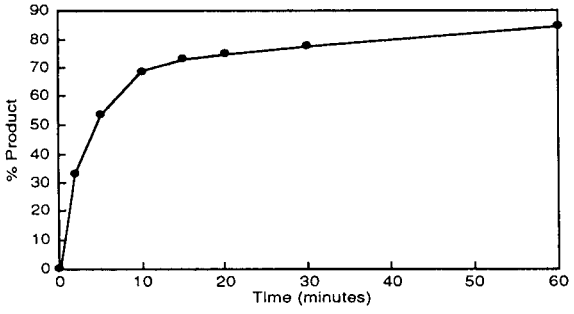


Figure 2. The formation of **6** from **7** in dimethoxyethane at 60° with etherate. The concentration of **6** was monitored by hplc.

None of the above conditions proved useful for the cyclization of compound **7**, and cobalt(II) and chloride were also ineffective. However, we found that compound **7** rapidly cyclized to the diaminoquinazoline **6** in the presence of boron trifluoride etherate, stannous chloride, or trimethylsilyl triflate in ethereal solvents such as dimethoxyethane, diglyme, or tetrahydrofuran. Our preferred conditions for cyclization were etherate in dimethoxyethane at 60°. The reaction occurred rapidly (30 minutes) under these conditions. As with the thermal cyclizations, the reaction was highly regioselective, and the linear isomer was not observed.

Using **7** as the starting material, we monitored the etherate-promoted cyclization by hplc. The results of a typical experiment are shown in Figure 2. In contrast to the results shown in Figure 1, the addition of etherate to the reaction mixture allowed an 85% yield in only 60 minutes with mild heating (60°).

In summary, this work has demonstrated that addition of boron trifluoride etherate enhances the cyclization of arylcyanoguanidine by improving both the reaction rate and the yield. Furthermore, the use of boron trifluoride etherate produces fewer side products, which facilitates product isolation and purification. We have prepared a variety of pyrroloquinazolines utilizing this method.

EXPERIMENTAL

Melting points were determined in capillary tubes on a Thomas-Hoover melting point apparatus and are uncorrected. Flash chromatography was carried out using E. Merck silica gel 60 (particle size 0.040-0.063 mm). The ^{1}H nmr spectra were measured at 200 MHz with a Varian XL-200 spectrometer. Chemical shifts are in parts per million (δ), relative to the observed solvent resonance (DMSO, 2.50). Mass spectral data and ^{1}H nmr properties of each analytical sample were compatible with its assigned structure. Amberlite resin, etherate, 5-aminoindole hydrochloride, and sodium dicyanamide were obtained from Aldrich Chemical Co. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, GA. All compounds were analyzed for C,H,N and gave combustion values within 0.4% of theoretical. Each compound moved as a single spot on tlc on Whatman silica gel 60A K6F plates with fluorescent indicator.

N-Cyano-*N'*-(1*H*-indol-5-yl)guanidine (**7**).

A suspension of 8.3 g (49 mmoles) of 5-aminoindole hydrochloride and 11 g (120 mmoles) of sodium dicyanamide in 100 ml of dimethylformamide was heated at 40° for 3 hours. The mixture was concentrated *in vacuo* and subsequently poured into 500 ml of water. The slurry was stirred for 2 hours, then the solid was isolated by filtration, washed with two 300-ml portions of water, and dried *in vacuo* to give 8.9 g of **7** as a tan solid (90% yield), mp 238-239°; ^{1}H nmr (DMSO-d_6): δ 6.4 (br s, 1H), 6.7 (br s, 2H), 6.95 (m, 1H), 7.3 (m, 2H), 7.45 (s, 1H), 8.9 (s, 1H), 11.1 (s, 1H).

Anal. Calcd. for $C_{10}H_9N_5$: C, 60.03; H, 4.59; N, 35.06. Found: C, 60.21; H, 4.60; N, 35.10.

1,3-Diamino-7*H*-pyrrolo[3,2-*f*]quinazoline (**6**).

Boron Trifluoride-Induced Cyclization.

A suspension of 1.0 g (5.0 mmoles) of *N*-cyano-*N'*-(1-*H*-indol-5-yl)guanidine **7** in 100 ml of dimethoxyethane was heated to 60° before 3.0 ml (24 mmoles) of boron trifluoride etherate was added. The mixture was stirred at 60° for 1.5 hours, and the solvent was removed *in vacuo* to leave a dark brown solid. Ethyl acetate (500 ml) was added, and the mixture was heated to boiling and filtered hot. The filtrate was concentrated to dryness and the residue was recrystallized twice from acetone to give

0.96 g of a tan solid. This solid was dissolved in methanol and treated with a small amount of alkaline decolorizing charcoal and briefly heated to boiling. The mixture was then vacuum filtered while hot and the filtrate was treated with Amberlite IRA-900 basic ion-exchange resin. The resin was filtered off and the solvent was removed *in vacuo* to leave 0.76 g (76% yield) of **6** as a white solid, mp 260-262° (lit mp 263-265); ms: m/z 200 (M^+_+1, 100); ^1H nmr (DMSO-d_6): δ 5.6 (br s, 2H), 6.6 (br s, 2H), 7.0 (m, 2H), 7.4 (m, 1H), 7.6 (d, J = 9 Hz, 1H), 11.5 (br s, 1H).

Anal. Calcd. for $C_{10}H_9N_5 \cdot 0.54H_2O$: C, 57.48; H, 4.86; N, 33.52. Found: C, 57.11; H, 4.48; N, 33.20.

Thermally Induced Cyclization.

A suspension of 166.0 g (0.83 mole) of *N*-cyano-*N'*-(1-*H*-indol-5-yl)-guanidine **7** in 2500 ml of diglyme was heated to reflux with stirring for 21 hours. The resulting dark mixture was cooled to 100° and filtered while hot to remove black solids. The filtrate was chilled to 30° and 143 ml (1.7-2.0 equivalents) glacial acetic acid was added. The mixture was further chilled to 0° and stirred 3 hours. The resulting orange precipitate was collected by filtration, washed with diethyl ether (2 x 250 ml), and dried to give 177.0 g of the diacetic acid salt (67% yield). A portion of the diacetic acid salt (4.48 g) was neutralized with aqueous potassium carbonate, and the resulting solid was recrystallized from ethyl acetate and 20:1 acetone/methanol to give the product **6** (58% yield). Analytical data were consistent with the expected product.

Acknowledgments.

We are indebted to B. Glover, R. Griffiths, and R. Hunter for their excellent technical assistance. We thank R. Crouch for providing the nmr tautomer assignment of **7**. Also, we thank D. Burns and R. Carmichael for assistance in preparing this manuscript.

REFERENCES AND NOTES

[1a] A. Rosowsky and E. J. Modest, *J. Org. Chem.*, **31**, 2607 (1966); [b] W. T. Colwell and J. I. DeGraw, U.S. Patent 4,818,753 (1989); *ChemAbstr.*, **111**, 115201u (1989); [c] P. Mamalis and L. M. Werbel, *Handbook of Experimental Pharmacology*, Vol **68/II**, W. Peters and W. H. G. Richards, eds, Springer-Verlag Publishing Co., New York, 1984, p 387; [d] E. F. Elslager and J. Davoll, *Lectures in Heterocyclic Chemistry*, R. N. Castle and L. B. Townsend, eds, HeteroCorporation, Provo, Utah, 1974, p S-97; [e] D. W. Fry and R. C. Jackson, *Cancer Metastasis Rev.*, **5**, 251 (1987); [f] P. J. O'Dwyer, D. D. Shoemaker, J. Plowman, J. Cradock, A. Grillo-Lopez and B. Leyland-Jones, *Invest. New Drugs*, **3**, 71 (1985).

[2a] A. Rosowsky and N. Papathanasopoulos, *J. Org. Chem.*, **39**, 3293 (1974); [b] A. Rosowsky, P. C. Huang, N. Papthanasopoulos and E. J. Modest, *J. Med. Chem.*, **17**, 1217 (1974); [c] Rosowsky and E. J. Modest, *J Heterocyclic Chem.*, **3**, 387 (1966).

[3] K. W. Ledig, US Patent 4,118561 (1978); *Chem. Abstr.*, **90**, 137852g (1979).

[4a] M. Lamant, *C R Acad. Sci. C*, 277, 319 (1973); [4b] K. Gewald, O. Calderon, H. Schäfer and U. Hain, *Liebigs Ann. Chem.*, 1390 (1984).

[5] J. Sepiol, *Synthesis*, 504 (1983).

[6] M. C. Desai and P. F. Thadeio, *Tetrahedron Letters*, **30**, 5223 (1989).