The Reaction of Pyridazinones with Nucleophiles. An Unusual Reaction with Cyanide

Edward W. Badger and Walter H. Moos*

Department of Chemistry, Warner-Lambert/Parke-Davis Pharmaceutical Research, Ann Arbor, Michigan 48105

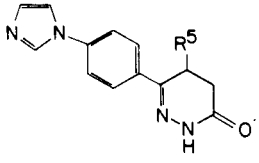
Received December 11, 1985

Studies on the synthesis of pyridazinone analogues of pyridone cardiotonics are reported. The synthetic scheme involves the reaction of pyridazinones and chloropyridazinones with nucleophiles. Addition occurred twice with cyanide as the nucleophile, thus providing a novel dicyanopyridazinone.

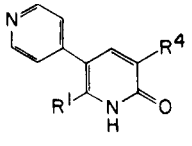
J. Heterocyclic Chem., **23**, 1515 (1986).

CI-914 (**1**), CI-930 (**2**), amrinone (**3**), and milrinone (**4**) are potent, novel cardiotonic agents which have recently progressed to clinical trials [1]. Because of chemical similarities between the pyridazinone and pyridone classes of cardiotonic agents, we became interested in the synthesis of amino- and cyanopyridazinones **5** and **6**.

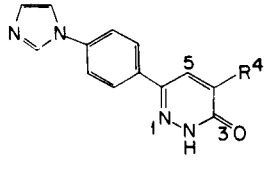
Synthesis of the amrinone analogue **5** was straightforward (Scheme 1). Treatment of pyridazinone **7** with hydrazine hydrate readily provides 4-aminopyridazinone **5**, as does Curtius rearrangement of hydrazide **8** [1-6]. Synthesis of the milrinone analogue **6**, however, has proved difficult, as described below.



1 CI-914 R^5=H
2 CI-930 R^5=CH_3



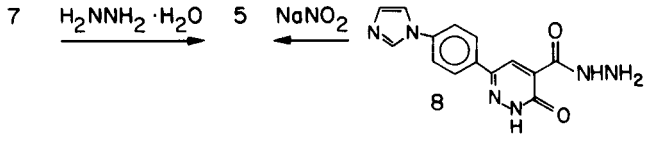
3 amrinone R^1=H, R^4=NH_2
4 milrinone R^1=CH_3, R^4=CN



5 R^4=NH_2
6 R^4=CN
7 R^4=H

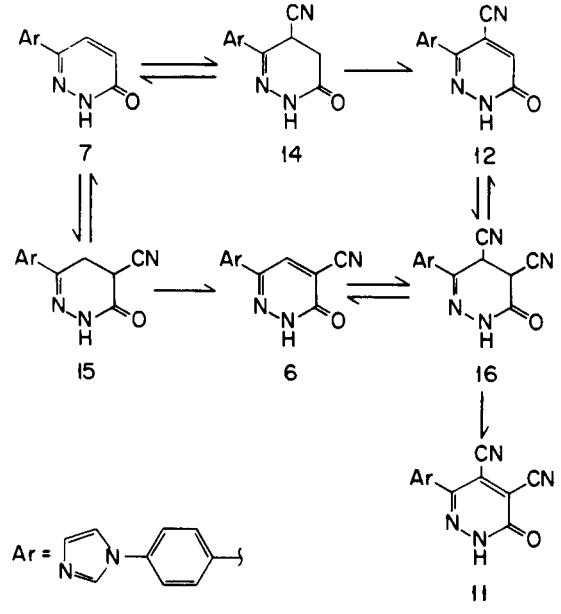
Numerous attempts to convert hydrazide **8** and amide **9** to nitrile **6** have been made [7], but with no success (Scheme 1). This led us to explore the reaction of pyridazinone **7** and chloropyridazinone **10** with cyanide (Schemes 2-4). Surprisingly, both reactions yield the same major product, albeit in low yield, namely the dicyanopyridazinone **11**. Only with very careful workup and chromatography can a monocyano adduct be isolated, and the process is capricious. Unfortunately, the monocyano adduct appears to be the isomeric **12** rather than the desired **6**, based upon a comparison of the hydrolysis product of **12** (**13**) with authentic amide **9**. To date, nitrile **6** remains elusive.

SCHEME 1

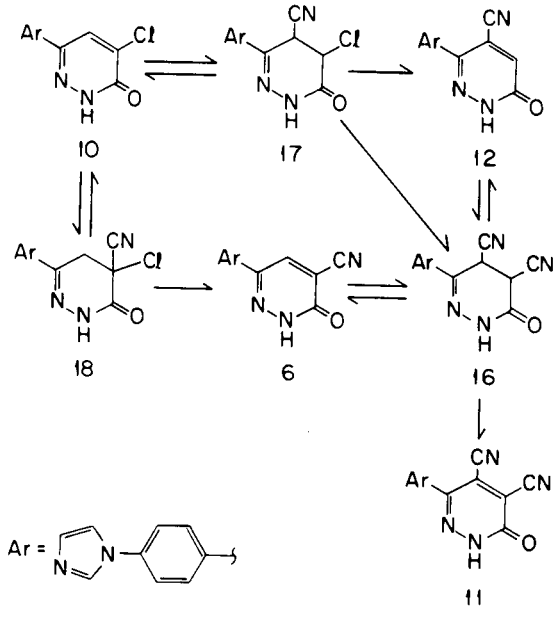


8 R=NH_2
9 R=H

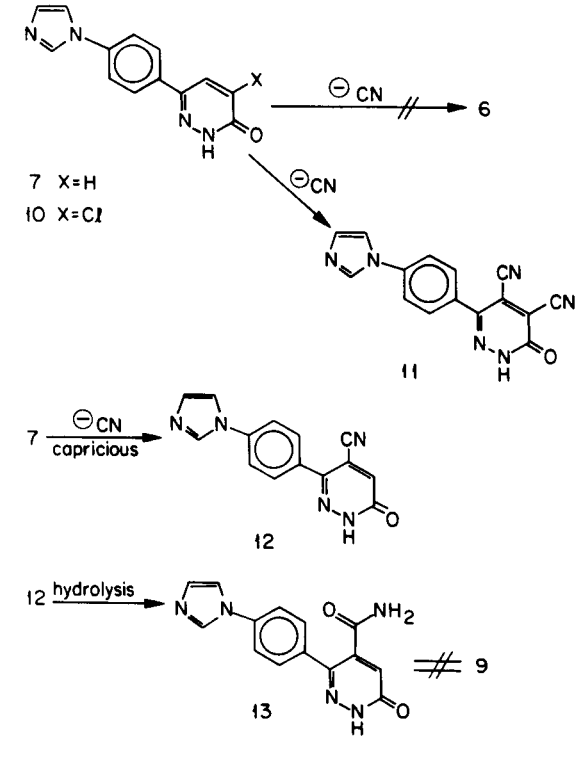
SCHEME 2



SCHEME 3



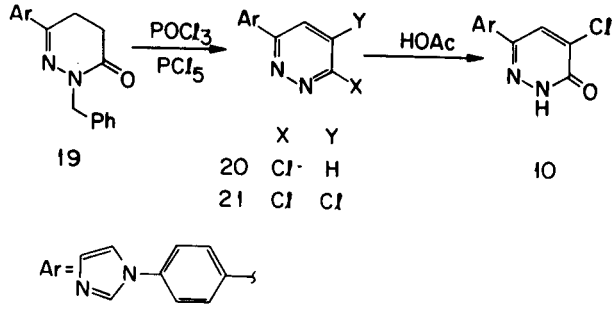
SCHEME 4



The possible mechanistic aspects of the cyanide reactions are interesting, but unproven. With pyridazinone **7**, it appears that **12** is an intermediate, because treatment of isolated **12** with cyanide affords **11**. However, the possibility remains that **6** is also an intermediate and has simply gone undetected. With the chloropyridazinone **10**, **12** is apparently not an intermediate based upon our inability to isolate it in this case and careful monitoring of the reaction with analytical liquid chromatography (alc). Finally, some comments on the oxidation step are in order. These reactions are normally run open to the atmosphere, a source of oxygen for the oxidation step. Running the reactions under an oxygen atmosphere causes an increased reaction rate, and under argon with carefully degassed dimethylsulfoxide the reaction proceeds very slowly. No reaction has been observed in a variety of other solvents, or with cuprous cyanide instead of potassium cyanide [8].

In summary, pyridazinones react readily with nucleophiles such as cyanide and hydrazine, and this methodology has allowed the synthesis of novel amino- and cyanopyridazinones. The biological data for these compounds will be reported elsewhere [11].

SCHEME 5



EXPERIMENTAL

The synthesis of compounds **7-9** and **19** has been described [1]. Chloropyridazinone **10** was prepared as outlined in Scheme 5 [3].

Toluene was dried over 4 Å molecular sieves [9]. Spectra were recorded with the following instruments as indicated: infrared (ir), potassium bromide unless otherwise noted, Nicolet interferometer, reported in cm^{-1}; ultraviolet (uv), methanol, Cary 118, λ max reported in nm; proton nuclear magnetic resonance (^1H nmr), dimethylsulfoxide-d_6 solvent, 90 MHz Varian EM-390 or Bruker WH-90, or 200 MHz Varian XL-200, reported as parts per million downfield from internal TMS, with couplings (J) in Hz; carbon nmr (^{13}C nmr), 50 MHz Varian XL-200, reported as in ^1H nmr; low resolution mass (ms), electron ionization, Finnigan 4521, reported as m/z (relative intensity). Elemental analyses were determined at Warner-Lambert/Parke-Davis.

Analytical liquid chromatography (alc) was performed with a Waters system consisting of 2 or 3 M-45 pumps, a U6K injector, a 680 automated gradient controller, and either a DuPont variable wavelength uv spectrophotometer operating at 254 or 280 nm or an Altex 153 fixed wavelength detector (254 nm). All final products were homogeneous by alc using one or more of the following conditions. Columns employed: (A) Altex Ultrasphere-Octyl, 5 μm, 4.6 x 250 mm; (B) Whatman Partisil PXS 10/25 ODS-2, 10 μm, 4.6 x 250 mm; (C) Hamilton PRP-1, 10 μm, 4.1 x 150 mm; (D) Alltech Silica, 10 μm, 4.6 x 250 mm. Solvents: (A) 1/1/1 water/methanol/acetonitrile; (B) 3/1 methanol/water; (C) 1/1 chloroform/ethyl acetate. Preparative liquid chromatography (plc) was performed on a Waters Prep 500A instrument, unless otherwise noted, under normal phase conditions, or by "flash"column chromatography (fcc) [10]. Analytical thin layer chromatography (tlc) was done with pre-coated glass plates (EM reagents silica gel 60 F-254).

Evaporations were performed under reduced pressure. All reactions were monitored by tlc and/or alc.

4-Amino-6-[4-(1-imidazolyl)phenyl]-3(2*H*)-pyridazinone (**5**).

Method 1.

A suspension of 10.0 g of pyridazinone **7** in 70 ml of hydrazine monohydrate was heated at 110° for 19 hours, cooled, filtered, and the solid washed with water 3 times and with ether to yield 7.22 g of a solid (78%). This solid was identical spectroscopically and chromatographically with material obtained from Curtius rearrangement of hydrazide **8** (see Method 2).

Method 2.

A slurry of 10.0 g of hydrazide **8**, 111 ml of water, and 195 ml of concentrated hydrochloric acid was cooled to 5°. To this slurry was added a solution of 5.6 g of sodium nitrite in 20 ml of water dropwise. After the addition, the cooling bath was removed, the mixture was allowed to warm slowly to room temperature, transferred to a large beaker, and heated on a steam bath until dissolution occurred. Continued heating was accompanied by gas evolution followed by precipitation. After cooling, the mixture was filtered, and the filtrate made basic (*p*H 11) *via* portionwise addition of concentrated ammonium hydroxide. The resulting suspension was filtered, and the solids recrystallized from methanol and purified further (fcc), eluting with 90/10/1 chloroform/methanol/ammonium hydroxide. The yield was 2.12 g (22%), mp 323-325°; ir: 3400, 3320, 3220, 1660, 1610, 1530, 1300, 1053; ^{1}H nmr: (90 MHz) δ 12.61 (s, 1H), 8.25 (s, 1H), 8.0-7.5 (superimposed doublets plus singlet, 5H, J = 16), 7.8 (s, 1H), 6.72 (s, 1H), 6.45 (br s, 2H); ^{13}C nmr: δ 155, 143, 143, 135, 133, 133, 128, 125, 118, 116, 96; ms: 253 (100); uv: λ max 268 (ϵ 47,400).

Anal. Calcd. for $C_{13}H_{11}N_5O$: C, 61.65; H, 4.38; N, 27.65. Found: C, 61.31; H, 4.61; N, 27.43.

4-Chloro-6-[4-(1-imidazolyl)phenyl]-3(2*H*)-pyridazinone (**10**).

A suspension of 25.66 g of dichloropyridazine **21** in 300 ml of glacial acetic acid was heated at reflux for 5 hours. The volatiles were removed *in vacuo* leaving a yellow oil which was made basic *via* portionwise addition of saturated aqueous potassium bicarbonate and filtered. The yellow solid was recrystallized from ethanol and purified (plc), eluting on two reverse phase columns with solvent system A. The major component (16.2 g, 67%) eluted second (t_R = 7.5 minutes); ir: 3230, 3130, 3110, 2930, 1680, 1615, 1600, 1580, 1530, 1305, 1070, 1060, 885, 835; ^{1}H nmr: (90 MHz) δ 13.7 (s, 1H), 8.55 (s, 1H), 8.38 (s, 1H), 8.2-8.0 (d, 2H, J = 5), 7.9-7.7 (d superimposed with s, 3H), 7.1 (s, 1H); ^{13}C nmr δ 155, 141, 136, 134, 133, 130, 128, 127, 125, 118, 116; ms: 272 (100); uv: λ max 272 (ϵ 28,000).

Anal. Calcd. for $C_{13}H_9ClN_4O$: C, 57.26; H, 3.33; N, 20.55. Found: C, 57.69; H, 3.45; N, 20.97.

4,5-Dicyano-6-[4-(1-imidazolyl)phenyl]-3(2*H*)-pyridazinone (**11**).

Method 1.

A solution of 5.0 g of pyridazinone **7** hydrochloride salt, 6.8 g of potassium cyanide, and 100 ml of dimethyl sulfoxide was heated at 50° for 19 hours and evaporated *in vacuo* to a brown slurry. The slurry was filtered, and the solid was recrystallized from 300 ml of ethanol, yielding 810 mg (14%). This solid was identical spectroscopically and chromatographically with material obtained from chloropyridazinone **10** (see Method 2).

Method 2.

A solution of 1.0 g of chloropyridazinone **10** and 1.17 g of potassium cyanide in 10 ml of dimethyl sulfoxide was heated at 60° for 1 hour, then cooled to room temperature and stirred 16 hours, and finally poured into water to yield an orange solution of *p*H 11. The *p*H was adjusted to 6.5 and the resulting suspension was filtered. The solid was washed with water, dissolved in 800 ml of ethanol and the solution treated with activated charcoal, filtered, concentrated to 125 ml, and kept at 4° for 16 hours to yield 160 mg (15%), mp 299-305°; ir: 2220-2200; ^{1}H nmr: (200 MHz) δ 8.33 (s, 1H), 7.88-7.84 (d, 2H, J = 9), 7.82 (s, 1H), 7.81-7.79 (d, 2H, J = 9), 7.11 (s, 1H); ms: 288 (90-100).

Anal. Calcd. for $C_{15}H_8N_6O\cdot 1/3EtOH$: C, 60.77; H, 3.47; N, 27.13. Found: C, 60.45; H, 3.08; N, 26.84.

5-Cyano-6-[4-(1-imidazolyl)phenyl]-3(2*H*)-pyridazinone (**12**).

A solution of 5.0 g of pyridazinone **7** and 6.8 g of potassium cyanide in 100 ml of dimethyl sulfoxide was heated at 55° for 19 hours, and poured into water. The suspension was filtered, and the solid was recrystallized from ethanol followed by recrystallization from hot aqueous 2% perchloric acid to yield 800 mg (10%) of the mono-perchlorate monohydrate, mp 278-280°; ir: 3160, 2960, 2880, 2240, 1670, 1545, 1100; ^{1}H nmr: (90 MHz) δ 14.0 (s, 1H), 9.68 (s, 1H), 8.85 (s, 1H), 8.3 (m, 1H), 8.2-7.7 (two superimposed doublets, 4H, J = 3, plus superimposed singlet); ^{13}C nmr: δ 155, 141, 136, 133, 130, 128, 125, 118, 116, 113, 112; ms: 263 (100); uv: λ max 360 (ϵ 1,575), λ max 280 (ϵ 21,700).

Anal. Calcd. for $C_{13}H_{11}N_5O\cdot HClO_4\cdot H_2O$: C, 44.00; H, 3.16; N, 18.32; H_2O, 4.7. Found: C, 44.27; H, 2.85; N, 18.29; H_2O, 3.8.

3,4-Dichloro-6-[4-(1-imidazolyl)phenyl]pyridazine (**21**).

A suspension of 1.0 g of benzylpyridazinone **19**, 5.0 g of phosphorus pentachloride, and 10 ml of phosphorus oxychloride was heated gently until dissolution accompanied by gas evolution occurred. The resulting solution was heated at reflux for 24 hours and poured into ice water. When all of the phosphorus oxychloride had decomposed, the *p*H was adjusted to 11 with concentrated ammonium hydroxide, and the mixture filtered. Recrystallization from ethanol yielded 120 mg (15%), mp 212-216°; ir: 1605, 1555, 1525, 1495, 1485, 1375, 1365, 1305, 1200, 1170, 1055, 960, 905, 840; ^{1}H nmr: (90 MHz) δ 8.8 (s, 1H), 8.45-8.2 (br d, 3H, J = 12), 8.2-8.0 (br, 3H), 7.1 (s, 1H); ms: 290 (100); uv: λ max 280 (ϵ 22,480).

Anal. Calcd. for $C_{13}H_8Cl_2N_4$: C, 53.63; H, 2.77; N, 19.24; Cl, 24.35. Found: C, 54.12; H, 3.07; N, 18.99; Cl, 24.84.

3-Chloro-6-[4-(1-imidazolyl)phenyl]pyridazine (**20**) was a by-product of this reaction.

REFERENCES AND NOTES

[1a] J. A. Bristol, I. Sircar, W. H. Moos, D. B. Evans, and R. E. Weishaar, *J. Med. Chem.*, **27**, 1099 (1984); [b] I. Sircar, B. L. Duell, G. Bobowski, J. A. Bristol, and D. B. Evans, *J. Med. Chem.*, **28**, 1405 (1985).

[2] B. Singh, *Heterocycles*, **22**, 1801 (1984).

[3] I. Sircar, *J. Heterocyclic Chem.*, **20**, 1473 (1983).

[4] D. R. Carver, T. D. Greenwood, J. S. Hubbard, A. P. Komin, Y. P. Sachdeva, and J. F. Wolfe, *J. Org. Chem.*, **48**, 1180 (1983).

[5] T. Matsuo, Y. Tsukamoto, T. Takagi, and H. Yginuma, *Chem. Pharm. Bull.*, **30**, 1030 (1982).

[6] J. D. Albright, F. J. McEvoy, and D. B. Moran, *J. Heterocyclic Chem.*, **15**, 881 (1978).

[7a] Pyridine/tosyl chloride: C. R. Stephens, E. J. Bianco, and F. J. Pilgrim, *J. Am. Chem. Soc.*, **77**, 1701 (1955); [b] thionyl chloride: H. Goldstein and R. Voegeli, *Helv. Chim. Acta*, **26**, 1125 (1943); J. A. Krynitsky and H. W. Carhart, *Org. Synth.*, Coll. Vol. IV, 436 (1963); C. R. Hauser and W. R. Brasen, *J. Am. Chem. Soc.*, **78**, 494 (1963); [c] thionyl chloride/*N,N*-dimethylformamide: A. S. Bailey, B. R. Henn, and J. M. Langdon, *Tetrahedron*, **19**, 161 (1963); J. C. Thurman, *Chem. Ind.*, 752 (1964); [d] phosphorus oxychloride: F. P. Doyle, W. Ferrier, D. O. Holland, M. D. Mehta, and J. H. C. Nayler, *J. Chem. Soc.*, 2853 (1956); P. F. Juby, T. W. Hudyma, M. Brown, J. M. Essery, and R. A. Partyka, *J. Med. Chem.*, **25**, 1145 (1982); K. Landenburg, M. Tishler, J. W. Wellman, and R. D. Babson, *J. Am. Chem. Soc.*, **66**, 1217 (1944); [e] acetic anhydride: P. Weiss, M. G. Cordasco, and L. Reiner, *J. Am. Chem. Soc.*, **71**, 2650 (1949); [f] butyl lithium: E. M. Kaiser and C. R. Hauser, *J. Org. Chem.*, **31**, 3873 (1966); E. M. Kaiser, R. L. Vaulx, and C. R. Hauser, *J. Org. Chem.*, **32**, 3240 (1967); [g] poly(trimethylsilyl)phosphoric acid $(PO_3SiMe_3)_n$: M. Yokoyama, S. Yoshida, and T. Imamoto, *Synthesis*, 591 (1982); [h] chlorosulfonyl isocyanate: G. Lohaus, *Chem. Ber.*, **100**, 2719, (1967).

[8] M. Newman and A. Boden, *J. Org. Chem.*, **26**, 2525 (1961).

[9] D. R. Burfield and R. H. Smithers, *J. Org. Chem.*, **48**, 2420 (1983).

[10] W. C. Still, M. Kahn and A. Mitra, *J. Org. Chem.*, **43**, 2923 (1978).

[11] See, for example, reference [1b].