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SYNTHESIS OF 2-AMINO-5-HYDROXY-4-PYRIMIDONES AND 5,6-BIHETEROARYLS USING *p*-NITROPHENYL 3-BROMO-2,2-DIETHOXYPROPIONATE (NPBDP)†

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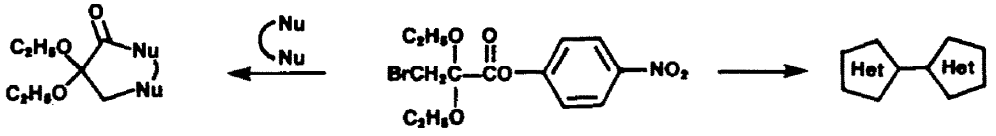
Abstract: The reaction of NPBDP with various guanidines affords, after formic acid hydrolysis, 2-amino-5-hydroxy-4-pyrimidones. Reaction of NPBDP with *o*-aminoheterocycles gives similar results. NPBDP is readily converted to the 3-amino-2-alkenenitrile, **10**, a key building block for the synthesis of 5,6-biheteroaryls.

p-Nitrophenyl 3-bromo-2,2-diethoxypropionate (NPBDP) has been demonstrated to be a valuable intermediate for the synthesis of highly functionalized small molecules as well as heterocycles.[1,2] Structurally, NPBDP can be considered as a masked α-bromoketone linked to an activated carboxylic acid. While intermolecular nucleophilic attack occurs exclusively at the activated acid, a bifunctional nucleophile, while first reacting at the activated acid site, can then produce an intramolecular nucleophilic displacement resulting in the formation of a heterocycle. NPBDP can also be viewed in another manner, specifically, as a molecule which contains the two units most commonly employed for the synthesis of five-membered heterocycles, i.e., the α-haloketone and activated acid. Separate chemical manipulation of each portion provides a wide variety of 5,5-biheteroaryls.

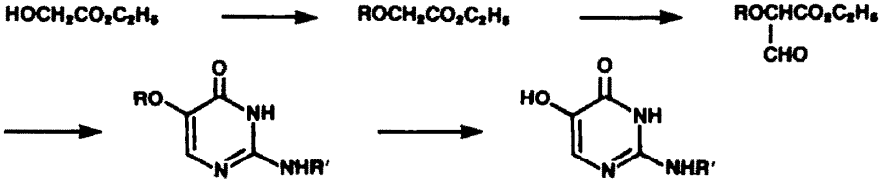


NPBDP

This paper describes two extensions of the utility of NPBDP. The first details the reaction of NPBDP with guanidines and derivatives, a method which provides a novel entry into a series of 2-amino-5-hydroxy-4-pyrimidones. The second extension involves the conversion of NPBDP to the 3-amino-2-alkenenitrile, 2-amino-4-bromo-1-cyano-3,3-diethoxy-1-butene, an intermediate useful for the synthesis of 5,6-biheteroaryls.

2-Amino-5-hydroxy-4-pyrimidones

In connection with a synthetic program designed to identify novel therapeutic agents, a versatile synthesis of 2-amino-5-hydroxy-4-pyrimidones was required. An established literature synthesis for this class of compounds involves a multistep sequence in which ethyl glycolate, as its O-protected ether, is condensed with ethyl formate, and this intermediate is reacted with guanidines. Deprotection then affords the desired compounds.[3]

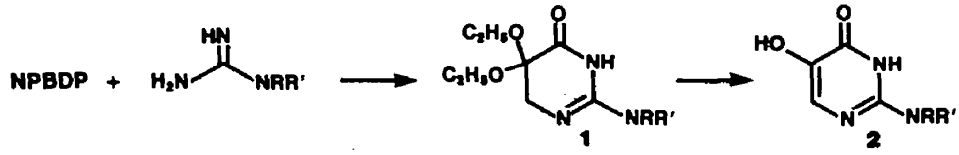


While this procedure is clearly useful, it suffers some drawbacks not the least of which is either the difficult removal of a protecting group (benzyl) or dealing with one which tends to be removed in the course of the synthesis (tetrahydropyranyl). A more attractive approach to these compounds involves utilizing the reactivity of NPBDP with a bifunctional nucleophile such as guanidine. Simple deketalization with formic acid would then provide the desired 2-amino-5-hydroxy-4-pyrimidones.

In fact, this proved to be the case. Treatment of NPBDP with N,N-dimethylguanidine in ethanol at room temperature afforded the uncyclized 1,2-adduct. This material, when heated at reflux in ethanol smoothly cyclized to give **1a** in good yield. Rather than isolate the initial adduct, it was simpler to carry out this reaction in refluxing ethanol and isolate **1a** directly from NPBDP. Reaction of **1a** in neat formic acid then afforded **2a** in modest overall yield. A summary of this reaction, as well as other examples, appears in the table. It should be noted that in one case, formic acid hydrolysis of **1a** provided, in addition to **2a**, a small amount of 2-N,N-dimethylamino-5-ethoxy-4-pyrimidone (**3**), which results from elimination of ethanol rather than deketalization. This type of byproduct was not detected in any other of the reactions in the table.

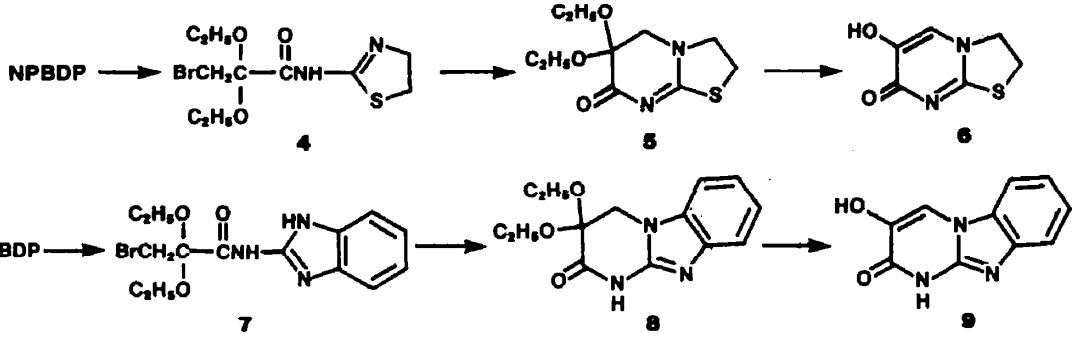
†It is with great pleasure that we dedicate this manuscript to Professor Edward C. Taylor, a valued mentor and friend, on the occasion of his sixty-fifth birthday.

Table. 2-Amino-5-hydroxy-4-pyrimidones



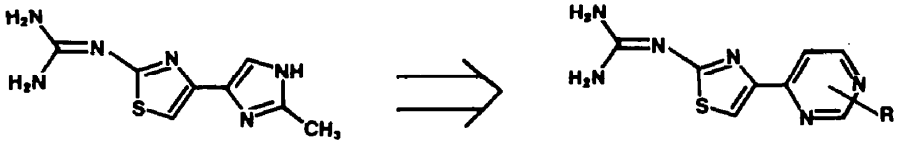
	R	R'	Yield (%)	Yield (%)
a.	CH_3	CH_3	73	62
b.	$CH_2C_6H_5$	H	75	47
c.	$C(CH_2)_2C_6H_5$ (CH3)	H	52	42
d.	$C(CH_2)_3CH(CH_3)_2$ (CH3)	H	74	34

This sequence can be further extended to prepare fused derivatives of 5-hydroxy-4-pyrimidones. Treatment of NPBDP with 2-aminothiazoline in pyridine gave 71% of adduct **4**. This could be cyclized with sodium ethoxide/ethanol to give **5** in 55% yield. Deketalization of **5** with formic acid afforded **6** in 75% yield. In a similar fashion, 2-aminobenzimidazole can be carried through this sequence to provide **9** via intermediates **7** and **8**.

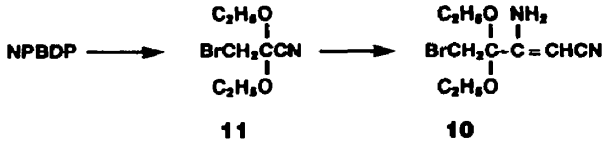


5,6-Biheteroaryls

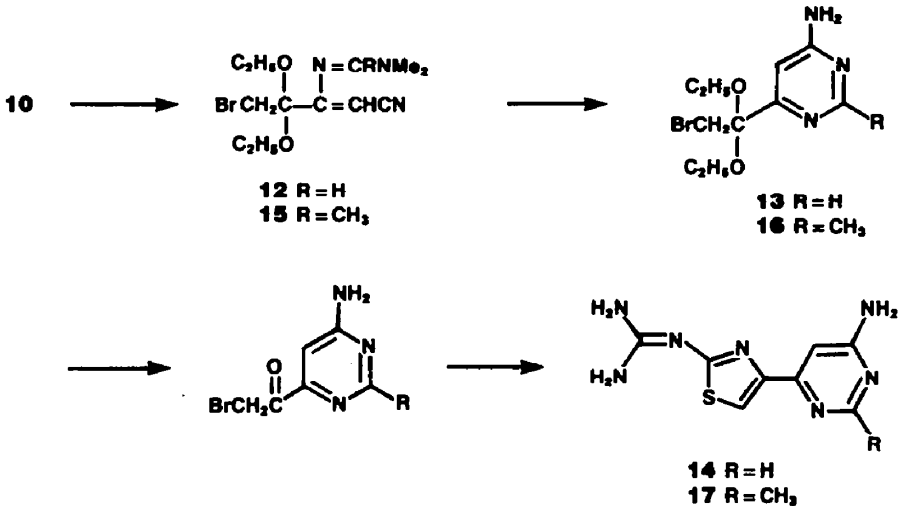
Previous work from these laboratories described a series of 2-guanidino-4-(heteroaryl)thiazoles which are novel histamine H_2-receptor antagonists.[4] The most potent of these was 2-guanidino-4-(2-methyl-4-imidazolyl)thiazoles, a 5,5-biheteroaryl. In developing structure-activity relationships in this series, NPBDP was used to prepare analogs in which both five-membered rings could be modified.[3] A natural extension of this work would be to prepare compounds in which the imidazole is replaced by six-membered rings, specifically pyrimidines.



One approach to these pyrimidines would involve conversion of the activated acid portion of NPBDP to a 3-amino-2-alkenenitrile, a known building block for pyrimidines.[5] Thus, a simple route to compound **10** was sought. An attractive approach to **10** was based on the recent synthesis of compounds of this type by Hiyama in which a highly selective cross-Thorpe was observed when reacting α-lithioacetonitrile with 2,2-dimethoxypropionitrile.[6] Application of the cross-Thorpe reaction to this case would involve utilizing 3-bromo-2,2-diethoxypropionitrile **11**, which is, in fact, readily available from NPBDP in 68% yield by reaction first with ammonia to give an intermediate amide which is dehydrated as described.[2] Reaction of **11** with α-lithioacetonitrile did afford the desired **10** as the only isolated product but, inexplicably, in low yield (20%). Various attempts made to improve this reaction were in vain. However, since this synthesis was simple to execute and since it readily provided multigram quantities of **10**, it well served our needs.



Subsequent conversion of **10** to the desired targets proved straightforward. Reaction of **10** with dimethylformamide dimethylacetal gave amidine **12** in 93% yield. Cyclization of **12** with ammonium acetate gave 69% of pyrimidine **13**, which was deprotected with hydrobromic acid and reacted with amidinothiourea to afford analog **14**. By repeating this sequence with dimethylacetamide dimethylacetal, the corresponding 2-methylpyrimidines were prepared.



Summary

This work further demonstrates the versatility of NPBDP in heterocyclic synthesis. NPBDP can be viewed as an equivalent of "$^{+}_{CH_2}\overset{O}{\overset{\|}{C}}\overset{O}{\overset{\|}{C}}$", and as such can be reacted with guanidines and *o*-aminoheterocycles to afford 5-hydroxy-4-pyrimidones and fused 5-hydroxy-4-pyrimidones, respectively. However, one can also consider NPBDP as a biheteroaryl building block, not only for 5,5-biheteroaryls but now also for 5,6-biheteroaryls through the intermediacy of compound **10**. NPBDP should continue to be a valuable intermediate in heterocyclic synthesis.

EXPERIMENTAL

General:

^{1}H NMR spectra were obtained on a Varian T-60 spectrometer; chemical shifts from tetramethylsilane are reported on the δ scale. IR spectra were recorded on a Perkin-Elmer 237B grating spectrophotometer. High resolution mass spectra were recorded on an AEI MS30 spectrometer. Melting points are uncorrected and were obtained in open capillaries on a Thomas-Hoover melting point apparatus. Solvents and reagents, including NPBDP (Aldrich), were commercially available, and, unless otherwise noted, were used directly.

General Procedure for the Synthesis of N-Substituted Guanidines

A mixture of 80 mmol of the appropriate amine, 80 mmol of 3,5-dimethylpyrazole-1-carboxamidine, 5 mL of acetic acid and 75 mL of toluene was heated at reflux for 16 h. The mixture was cooled, the precipitate was collected, and the material was dried *in vacuo*, thereby affording 80-90% yields of the substituted guanidine as its acetate salt. These guanidines were used without further purification.

2-N,N-Dimethylamino-5-hydroxy-4-pyrimidone (2a)

Sodium (1.5 g, 66 mmol) was dissolved in 100 mL of absolute ethanol under a nitrogen atmosphere and 12.2 g (66 mmol) of N,N-dimethylguanidine sulfate was added, and this mixture was stirred at room temperature for 1 h. The insolubles were removed by filtration and the filtrate was added to a solution of 8.0 g (22 mmol) of NPBDP in 150 mL of absolute ethanol. After heating this mixture at reflux for 16 h, the mixture was concentrated. The residue was dissolved in 150 mL of saturated sodium bicarbonate solution, and stirred for 15 min. The aqueous solution was brought to pH 2 with 6N hydrochloric acid and then extracted with ethyl acetate (4 x 100 mL). The combined extracts were dried (anhyd. Na_2SO_4), filtered, and evaporated leaving a mixture of *p*-nitrophenol and **1a**. These were readily separated by flash column chromatography using 10:1 chloroform/methanol as eluent to afford 3.71 g (73%) of **1a** as a white solid, mp 160-164 °C; NMR ($CDCl_3$): 8.60 (b, 1H); 3.9-3.4 (q + s, 6H); 3.27 (s, 6H); 1.17 (t, 6H). HRMS obsd. M$^+$ m/z 229.1433; $C_{10}H_{19}N_3O_3$ calcd. 229.1426. This material (3.0 g, 13 mmol) was added to 100 mL of formic acid and heated at reflux for 19 h. The mixture was concentrated, the residue triturated with ether, and the solid was collected by filtration. The product was separated from a small amount of a less polar material by flash chromatography over silica gel using 5:1 chloroform/methanol

as eluent. The less polar material amounted to 0.37 g (14%) of 2-dimethylamino-5-ethoxy-4-pyrimidone (3), mp 166-168°C; NMR ($CDCl_3$): 7.37 (s, 1H); 3.90 (q, 2H); 3.10 (s, 6H); 1.28 (t, 3H). HRMS obsd. M^+ m/z 183.1017; $C_8H_{13}N_3O_2$ calcd. 183.1011.

Anal. Calcd. for $C_8H_{13}N_3O_2$: C, 52.44; H, 7.15; N, 22.94. Found: C, 51.93; H, 7.00; N, 22.57.

The product amounted to 1.25 g (62%) of **2a**, mp 250-253°C; NMR (d_6-DMSO): 7.6-7.2 (b + s, 3H); 3.15 (s, 6H). HRMS obsd. M^+ m/z 155.0676; $C_6H_9N_3O_2$ calcd. 155.0697. A sample of this material was converted to its HBr salt for analysis.

Anal. Calcd. for $C_6H_9N_3O_2 \cdot 1.5$ HBr: C, 26.01; H, 3.81; N, 15.16. Found: C, 26.30; H, 3.83; N, 15.16.

2-N-Benzylamino-5-hydroxy-4-pyrimidone (2b)

Sodium (0.57 g, 24.8 mmol) was dissolved in 50 mL of absolute ethanol, and 5.20 g (24.8 mmol) of N-benzylguanidine acetate was added. The mixture was stirred at room temperature for 1 h, and filtered to remove insolubles. A solution of 3.0 g (8.3 mmol) of NPBDP in 50 mL of ethanol was added to the filtrate and this was heated at reflux for 16 h. The mixture was concentrated and the residue was dissolved in 100 mL of saturated sodium bicarbonate solution and stirred at room temperature for 15 min. The aqueous mixture was brought to pH 2 with 6N hydrochloric acid, then extracted with ethyl acetate (4 x 100 mL). The combined extracts were dried (anhyd. Na_2SO_4), filtered, and evaporated leaving a mixture of *p*-nitrophenol and the product. Chromatography over silica gel using 20:1 chloroform/methanol as eluent afforded 1.81 g (75%) of **1b**, mp 213-214°C (acetonitrile); NMR ($CDCl_3$): 7.26 (s, 5H); 4.60 (bs, 2H); 3.8-3.4 (q + s, 6H); 1.14 (t, 6H). HRMS obsd. M^+ m/z 291.1614; $C_{15}H_{21}N_3O_3$ calcd. 291.1587.

Anal. Calcd. for $C_{15}H_{21}N_3O_3 \cdot 1/4\ H_2O$: C, 60.89; H, 7.32; N, 14.20. Found: C, 61.11; H, 7.18; N, 14.14.

A mixture of **1b** (1.0 g, 3.4 mmol) in 50 mL of formic acid was heated at reflux for 16 h. The mixture was concentrated and the residue was triturated with saturated sodium bicarbonate solution, collected by filtration, washed with water, and dried *in vacuo* to afford 0.35 g (47%) of **2b**, mp 197-200°C; NMR (d_6-DMSO): 7.13 (s, 5H); 7.02 (s, 1H); 4.38 (bs, 2H). HRMS obsd. M^+ m/z 217.0831; $C_{11}H_{11}N_3O_2$ calcd. 217.0855.

Anal. Calcd. for $C_{11}H_{11}N_3O_2 \cdot 1/4\ H_2O$: C, 59.58; H, 5.23; N, 18.95. Found: C, 59.93; H, 5.14; N, 18.80.

2-N-(4-Phenyl-2-butylamino)-5-hydroxy-4-pyrimidone (2c)

Using the same procedure described for the synthesis of **1b**, NPBDP was converted to **1c** in 52% yield, mp 180-183°C; NMR ($CDCl_3$): 8.95 (bs, 1H); 7.16 (s, 5H); 4.1-3.9 (m, 1H); 3.7-3.4 (q + s, 6H); 2.8-2.6 (m, 2H); 1.9-1.7 (m, 2H); 1.28 (d, 3H); 1.14 (t, 6H). HRMS obsd. M^+ m/z 333.2026; $C_{18}H_{27}N_3O_3$ calcd. 333.2053.

Anal. Calcd. for $C_{18}H_{27}N_3O_3 \cdot 1/2\ H_2O$: C, 63.13; H, 8.24; N, 12.27. Found: C, 63.32; H, 7.77; N, 12.22.

Using the same procedure described for the synthesis of **2b**, **1c** was allowed to react with formic acid to afford 42% of **2c**, mp 121-123°C (recrystallized from toluene); NMR (CD_3CO_2D): 7.33 (s, 1H); 7.2-7.0 (m, 5H); 3.7 (m, 1H); 2.6 (m, 2H); 1.9 (m, 2H); 1.21 (d, 3H). HRMS obsd. M^+ m/z 259.1335; $C_{14}H_{17}N_3O_2$ calcd. 259.1320.

2-N-(6-Methyl-2-heptylamino)-5-hydroxy-4-pyrimidone (2d)

Using the same procedure described for the synthesis of **1b**, NPBDP was converted to **1d** in 74% yield, mp 170-172°C (recrystallized from acetonitrile); NMR ($CDCl_3$): 3.9-3.4 (overlap of q, s, m, 7H); 1.6-1.0 (overlap of d, t, m, 16H); 0.82 (d, 6H). HRMS obsd. M^+ m/z 313.2360; $C_{16}H_{31}N_3O_3$ calcd. 313.2367.

Anal. Calcd. for $C_{16}H_{31}N_3O_3$: C,61.31; H, 9.98; H, 13.41. Found: C, 60.87; H, 9.87; N, 13.22.

Using the same procedure described for the synthesis of **2b**, **1d** was allowed to react with formic acid to afford 34% of **2d**, mp 96-100°C (recrystallized from acetonitrile); NMR (d_6-DMSO): 7.89 (s, 1H); 3.94 (m, 1H); 1.6-1.2 (m, 7H); 1.16 (d, 3H); 0.85 (d, 6H). HRMS obsd. M^+ m/z 239.1622; $C_{12}H_{21}N_3O_2$ calcd. 239.1635.

Anal. Calcd. for $C_{12}H_{21}N_3O_2$: C, 60.22; H, 8.84; N, 17.56. Found: C, 59.78; H, 8.95; N, 17.31.

2-N-(3-Bromo-2,2-diethoxypropionoyl)aminothiazoline (4)

2-Aminothiazoline (8.50 g, 83.2 mmol) was dissolved in 100 mL of pyridine under a nitrogen atmosphere. To this was added 10.0 g (27.6 mmol) of NPBDP and the mixture was stirred at room temperature for 0.5 h. The mixture was concentrated and the residue was dissolved in 100 mL of saturated sodium bicarbonate solution and stirred for 15 min. This solution was acidified to pH 2 with 6N hydrochloric acid, then extracted with ethyl acetate (4 x 100 mL). The combined

extracts were dried (anhyd. Na_2SO_4), filtered, and evaporated leaving a mixture of *p*-nitrophenol and the product. Separation by column chromatography over silica gel using chloroform as eluent afforded 6.34 g (71%) of **4** as a white solid, mp 122-123°C; NMR ($CDCl_3$): 3.94 (q, 2H); 3.59 (s, 2H); 3.8-3.2 (overlapping q, 4H); 1.23 (t, 3H). HRMS obsd. M^+ m/z 326.0096; $C_{10}H_{17}BrN_2O_3S$ calcd. 326.0123.

6,6-Diethoxy-2,3,6,7-tetrahydrothiazolo-[3,2-a]-7-pyrimidone (5)

Sodium (0.24 g, 10.4 mmol) was dissolved in 80 mL of abs. ethanol under a nitrogen atmosphere, 3.4 g (10.4 mmol) of **4** was added, and the mixture was heated at reflux for 16 h. The mixture was cooled, then concentrated. The residue was taken up into 100 mL of saturated sodium bicarbonate solution, stirred for 15 min, then extracted with ethyl acetate (4 x 100 mL). The combined extracts were dried (anhyd. Na_2SO_4), filtered, and evaporated leaving a yellow solid. Recrystallization from isopropyl ether then afforded 1.43 g (55%) of **5**, mp 85-86°C; NMR ($CDCl_3$): 4.01 (q, 2H); 3.73 (s, 2H); 3.63 (q, 4H); 3.27 (q, 2H); 1.19 (t, 6H). HRMS obsd. M^+ m/z 244.0823; $C_{10}H_{16}N_2O_3S$ calcd. 244.0880.

Anal. Calcd. for $C_{10}H_{16}N_2O_3S$: C, 49.16; H, 6.60; N, 11.47. Found: C, 49.06; H, 6.58; N, 11.37.

6-Hydroxy-2,3-dihydrothiazolo-[3,2-a]-7-pyrimidone (6)

A mixture of 0.70 g (2.86 mmol) of **5** in 10 mL of formic acid was heated at reflux for 16 h. The mixture was cooled, then concentrated to afford a gummy solid. Trituration with chloroform yielded a white solid which was filtered, washed with chloroform, then dried *in vacuo* to afford 0.36 g (75%) of **6** as a white solid, mp 242-244°C; NMR (d_6-DMSO): 7.51 (s, 1H); 4.29 (t, 2H); 4.02 (t, 2H). HRMS obsd. M^+ m/z 170.0086; $C_6H_6N_2O_2S$ calcd. 170.0152.

2-N-(3-Bromo-2,2-diethoxypropionyl)aminobenzimidazole (7)

2-Aminobenzimidazole (1.10 g, 8.26 mmol) was dissolved in 20 mL of pyridine under a nitrogen atmosphere and to this was added 1.00 g (2.76 mmol) of NPBDP. The mixture was heated at 105°C (external) for 2 h, cooled, then concentrated. The residue was dissolved in 30 mL of saturated sodium bicarbonate solution, stirred for 15 min, then brought to pH 2 with 6N hydrochloric acid. The aqueous mixture was extracted with ethyl acetate (4 x 50 mL) and the combined extracts were dried (anhyd. Na_2SO_4), filtered and evaporated leaving a mixture of *p*-nitrophenol and the product. Separation by flash column chromatography using 50:1 chloroform/methanol as eluent afforded a yellow solid. Recrystallization from acetonitrile afforded 0.70 g (71%) of **7**, mp 214-216°C; NMR ($CDCl_3$): 7.5-7.0 (m, 4H); 3.64 (s, 2H); 3.52 (q, 4H); 1.27 (t, 6H). HRMS obsd. M^+ m/z 357.0325; $C_{14}H_{18}BrN_3O_3$ calcd. 357.0536.

Anal. Calcd. for $C_{14}H_{18}BrN_3O_3 \cdot 1/2\ H_2O$: C, 46.04; H, 5.24; N, 11.50. Found: C, 46.44; H, 5.06; N, 11.45.

3,3-Diethoxy-1,4-Dihydro-2-pyrimidinono[1,2-a]benzimidazole (8)

Sodium (0.11 g, 4.7 mmol) was dissolved in 40 mL of abs. ethanol under a nitrogen atmosphere, and 1.65 g (4.6 mmol) of **7** in 20 mL of abs. ethanol was added. This mixture was heated at reflux for 40 h. The mixture was cooled, then concentrated and the residue chromatographed directly over silica gel using 20:1 chloroform/methanol as eluent to give a white solid. Recrystallization from ethyl acetate afforded 0.79 g (62%) of **8**, mp 192-195°C; NMR (CD_3OD): 7.2-7.0 (m, 4H); 3.74 (s, 2H); 3.62 (q, 4H); 1.29 (t, 6H). HRMS obsd. M^+ m/z 275.1263; $C_{14}H_{17}N_3O_3$ calcd. 275.1275.

3-Hydroxy-2-pyrimidono[1,2-a]benzimidazole (9)

A mixture of 1.2 g (4.3 mmol) of **8** in 10 mL of formic acid was heated at reflux for 20 h. The mixture was concentrated and the residue triturated with chloroform. The resulting solid was collected and dried *in vacuo* to give 0.35 g (40%) of **9**, mp >280°C; NMR (d_6-DMSO): 7.52 (s, 1H); 7.4-7.1 (m, 4H). HRMS obsd. M^+ m/z 201.0514; $C_{10}H_7N_3O_2$ calcd. 201.0538.

2-Amino-4-bromo-1-cyano-3,3-diethoxy-1-butene (10)

A solution of 3.70 g (.090 m) of dry acetonitrile in 280 mL of dry tetrahydrofuran (THF) was stirred at -70°C under a nitrogen atmosphere and 43 mL of a 2.1M solution of n-butyl lithium in hexane was added dropwise over 0.5 h, keeping the temperature at -70°C. After addition was complete, the mixture was stirred at -70°C for 15 min, then a solution of 20.0 g (0.090 m) of 3-bromo-2,2-diethoxypropionitrile[2] in 40 mL of dry THF was added dropwise over 40 min, again keeping the temperature at -70°C. After stirring an additional 15 min at -70°C, the mixture was allowed to warm to room temperature, then poured into 320 mL of saturated ammonium chloride solution. The aqueous mixture was extracted with ether (3 x 150 mL), and the combined extracts were dried (anhyd. Na_2SO_4), filtered, and evaporated leaving an oil. Chromatography over silica gel using 6:1 hexane/ethyl acetate afforded 4.61 g (20%) of **10** as a pale yellow solid, mp 93-95°C; NMR ($CDCl_3$): 5.23 (bs, 2H); 4.27 (s, 1H); 3.60 (q, 4H); 3.45 (s, 2H); 1.27 (t, 6H). HRMS obsd. M^+ m/z 262.0338; $C_9H_{15}BrN_2O_2$ calcd. 262.0317.

Anal. Calcd. for $C_9H_{15}BrN_2O_2$: C, 41.08; H, 5.75; N, 10.65. Found: 41.02; H, 5.60; N, 10.54.

4-Bromo-1-cyano-3,3-diethoxy-2-N-(N',N'-dimethylformamidino)-1-butene (12)

A mixture of 1.75 g (6.7 mmol) of **10** and 60 mL of N,N-dimethylformamide dimethyl acetal was stirred at room temperature for 16 h. The mixture was concentrated and the residue was triturated seven times with 15 mL portions of boiling hexane. Concentration of the combined extracts afforded a yellow solid. Recrystallization from hexane afforded 1.99 g (93%) of **12** as a yellow solid, mp 104.5-105.5°C; NMR ($CDCl_3$): 7.67 (s, 1H); 5.13 (s, 1H); 3.50 (s, 2H); 3.42 (q, 4H); 3.03 (s, 3H); 3.00 (s, 3H); 1.16 (t, 6H).

Anal. Calcd. for $C_{12}H_{20}BrN_3O_2$: C, 45.29; H, 6.333; N, 13.21. Found: C, 45.71; H, 6.53; N, 13.06.

4-Bromo-1-cyano-3,3-diethoxy-2-N-(N',N'-dimethylacetamidino)-1-butene (15)

A mixture of 1.69 g (6.4 mmol) of **10** and 10 mL of N,N-dimethylacetamide dimethylacetal was heated 110°C for 16 h. The mixture was concentrated and the residue was chromatographed over silica gel using 5:1 hexane/ethyl acetate as eluent to afford 1.85 g (87%) of **15** as a white solid, mp 67-68.5°C; NMR ($CDCl_3$): 5.07 (s, 1H); 3.52 (q, 4H); 3.43 (s, 2H); 3.05 (s,6H); 2.16 (s, 3H); 1.23 (t, 6H).

6-Amino-4-(2-bromo-1,1-diethoxyethyl)pyrimidine (13)

A mixture of 1.00 g (3.1 mmol) of **12**, 4.1 g (51 mmol) of ammonium acetate, and 15 mL of abs. ethanol was heated at reflux for 3 h. The mixture was concentrated and the residue was triturated with ethyl acetate. The ethyl acetate solution was filtered from the insolubles, and the filtrate was washed with saturated sodium bicarbonate solution (3 x 15 mL). Concentration of the ethyl acetate solution afforded a solid which was recrystallized from 1:1 toluene/cyclohexane to give 0.63 g (69%) of **13** as a beige solid, mp 163-164°C; NMR ($CDCl_3$): 8.47 (s, 1H); 6.86 (s, 1H); 6.0 (bs, 2H); 3.81 (s, 2H); 3.6-3.2 (m, 4H); 1.17 (t, 6H).

6-Amino-4-(2-bromo-1,1-diethoxyethyl)-2-methylpyrimidine (16)

Using the same procedure outlined above for the synthesis of **13**, acetamidino derivative **15** was converted into **16** in 66% yield, mp 152.5-155°C, NMR ($CDCl_3$): 6.75 (s, 1H); 5.40 (bs, 2H); 3.90 (s, 2H); 3.8-3.2 (m, 4H); 2.59 (s, 3H); 1.28 (t, 6H).

2-Guanidino-4-(4-amino-6-pyrimidyl)thiazole-HBr (14)

A mixture of 0.93 g (3.2 mmol) of **13** and 18 mL of 48% hydrobromic acid was stirred at room temperature for 1 h. The mixture was concentrated and the solid residue was triturated with saturated sodium bicarbonate solution. The resulting slurry was filtered, washed with water, then dried *in vacuo* to afford 0.62 g (89%) of the intermediate α-bromoketone; NMR (d_6-DMSO): 8.39 (s, 1H); 7.5-7.2 (b, 2H); 6.86 (s, 1H); 4.78 (s, 2H). This material (0.26 g, 1.2 mmol) was dissolved in 7 mL of acetone, 0.14 g (1.2 mmol) of amidinothiourea was added and the mixture was heated to reflux for 1 h. The resulting precipitate was filtered, washed with acetone, and dried *in vacuo* to afford 0.35 g (88%) of pure **14**, mp >250°C; NMR (d_6-DMSO): 8.41 (s, 1H); 8.0 (b, 4H); 7.3 (b, 2H); 7.18 (s, 1H). HRMS obsd. M^+ m/z 235.0622; $C_8H_9N_7S$ calcd. 235.0639.

Anal. Calcd. for $C_8H_9N_7S \cdot HBr \cdot H_2O$: C, 28.75; H, 3.62; N, 29.34; S, 9.59. Found: C, 28.77; H, 3.59; N, 28.86; S, 9.47.

2-Guanidino-4-(4-amino-2-methyl-6-pyrimidyl)thiazole·HBr (17)

A mixture of 1.13 g (3.7 mmol) of **16** and 20 mL of 48% hydrobromic acid was stirred at room temperature for 2.5 h. The mixture was concentrated and the solid residue was triturated with saturated sodium bicarbonate solution. The resulting slurry was filtered, washed well with water, then dried *in vacuo* to afford 0.77 g (90%) of the intermediate α-bromoketone; NMR (CD_3OD): 6.82 (s, 1H); 4.84 (s, 2H); 2.46 (s, 3H). This material (0.23 g, 1.0 mmol) was dissolved in 7 mL of acetone, 0.12 g (1.0 mmol) of amidinothiourea was added, and the mixture was heated at reflux for 1 h. The resulting precipitate was filtered, washed with acetone, and dried *in vacuo* to afford 0.32 g (90%) of pure **17**, mp >250°C; NMR (d_6 DMSO, D_2O): 8.01 (s, 1H); 7.07 (s, 1H); 2.48 (s, 3H). HRMS obsd. M^+ m/z 249.0817; $C_9H_{11}N_7S$ calcd. 249.0797.

Anal. Calcd. for $C_9H_{11}N_7S \cdot HBr \cdot H_2O$: C, 31.04; H, 4.05; N, 28.16; S, 9.20. Found: C, 31.50; H, 3.74; N, 28.89; S, 9.54.

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