An Improved Synthesis of 2-Amino-5-[(4-chlorophenyl)thio]-4-morpholinopyrimidine (BW 394U) - A Potential Antisenility Agent

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This paper describes the synthesis of 2-amino-5-[(4-chlorophenyl)thio]-4-morpholinopyrimidine (BW 394U, compound **4**), a potential antisenility agent. The key intermediates **3a/3b** were obtained from an *in situ*-generated Vilsmeier-Haack reagent that simultaneously protected the 2-amino group prior to further manipulations. Displacement of the chloro group in **3a** gave **4** in 40% yield and 4-dimethylamino analogue **5**. However, displacement of **3b** with morpholine followed by treatment with aqueous base gave **4** in 74% yield.

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Introduction.

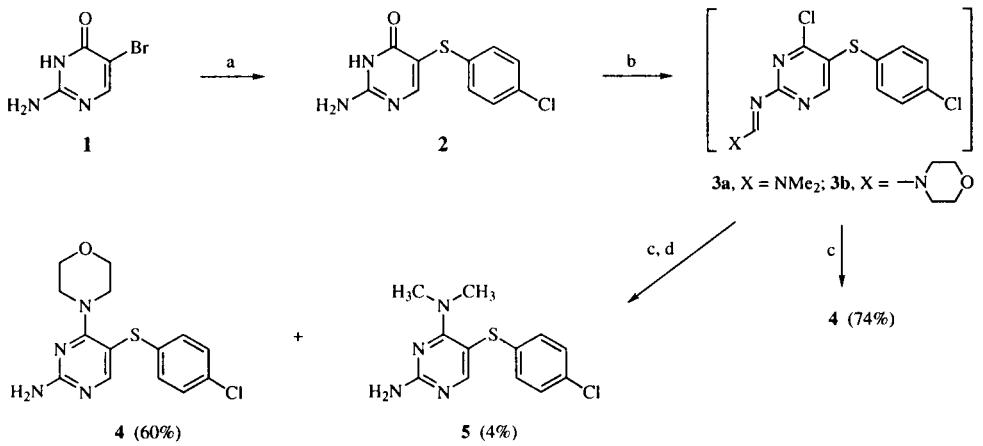
Age-related dementia such as Alzheimer's disease is a debilitating mental impairment for which there is no effective cure. Although the etiology of Alzheimer's disease is not fully understood, the illness is characterized by a loss of brain neurons [1] and drastic changes in brain neurotransmitters, including acetylcholine [2-3]. Ideally, drugs for treating dementia would prevent the loss of neurons while maintaining a steady supply of neurotransmitters. Intensive research activity focused on enhancing brain neurotransmitters has resulted in the approval of tacrine [4] and donepezil [5], both of which inhibit acetylcholinesterase, the enzyme responsible for the breakdown of acetylcholine.

In the search for compounds with unique mechanisms of action, 2-amino-5-[(4-chlorophenyl)thio]-4-morpholinopyrimidine (BW 394U, compound **4** [6]) was found to stimulate choline acetyltransferase [7], the enzyme that synthesizes acetylcholine. Additionally, compound **4** enhanced neuron outgrowth by potentiating the action of nerve growth factor (NGF) [1,7]. The nerve growth factor regulates growth and survival of neurons; however, this brain neurotrophic factor has limited potential because of its inability to cross the blood brain barrier [8]. Consequently, we needed to synthesize a large quantity of **4** for *in vivo* assays and to further assess its therapeutic utility for the treatment of Alzheimer's disease and dementia in general.

The previously reported synthesis of **4** [9] suffered from a number of liabilities including inconsistent and poor yields. Furthermore, the use of phosphoryl chloride for the chlorination of compound **2** is encumbered by concomitant reaction with the unprotected 2-amino group, which complicates purification of the desired pyrimidine **4**.

We report herein an improved synthesis of **4** (Scheme I) [10]. The key step in our synthesis was the use of an *in situ*-generated Vilsmeier-Haack [11] reagent in the chlorination of pyrimidine **2**, which simultaneously protected the 2-amino moiety and facilitated manipulation of the chloro group. Our synthesis began with the displacement of the bromo group in **1** [12] by 4-chlorophenylthiolate in *N,N*-dimethylformamide instead of ethylene glycol; this dramatically improved the

Scheme I



a) 4-ClC$_6$H$_4$SH, K_2CO_3, DMF; b) Method A: DMF, $SOCl_2$, Method B: Formylmorpholine, $(CO)_2Cl_2$; c) Morpholine, absolute EtOH; d) NaOH, H_2O

yield of 2-amino-5-[(4-chlorophenyl)thio]-4(3*H*)-pyrimidone (**2**) from 40% to 92%.

Chlorination of compound **2** with the Vilsmeyer-Haack reagent generated from thionyl chloride and *N,N*-dimethylformamide (Method A) gave intermediate **3a**. Treatment of **3a** with morpholine led to **4** (40%) and 4-dimethylamino analogue **5** after a difficult chromatographic separation. We believe that transamination of **3a** with morpholine at the amidine moiety generated dimethylamine, which competed with morpholine in chlorine displacement to give **5**.

To circumvent the formation of **5**, pyrimidine **2** was chlorinated with a Vilsmeier-Haack reagent generated from *N*-formylmorpholine and oxalyl chloride (Method B) [13]. *In situ* chloro substitution of **3b** [14] with morpholine and subsequent *N*-deprotection with aqueous base provided target **4** in 74% yield.

In summary, we have described an improved synthesis of compound **4** (BW 394U). The key innovation in the synthesis was the chlorination of intermediate **2** by an *in situ*-generated Vilsmeier-Haack type reagent which simultaneously protected the 2-amino group in **2**. We have also improved on the yield of **2** by using *N,N*-dimethylformamide instead of ethylene glycol as the solvent. The utility of BW 394U and its analogues as potential antisenility agents will be reported in due course.

EXPERIMENTAL

General.

Melting points were determined on a Thomas Hoover melting point apparatus and are uncorrected. ^{1}H nmrspectra were recorded on a Varian XL-300 NMRspectrometer. Mass spectral data were obtained from Oneida Research Services. Microanalyses were provided by Atlantic Microlab. All commercial reagents were used without further purification. High pressure chromatography (HPLC) was performed using Nova-Pak C18 with 60% methanol/water, 0.1% trifluoroacetic acid, 0.1% triethylamine as the mobile phase. Flash column chromatography was performed according to reference [15].

2-Amino-5-[(4-chlorophenyl)thio]-4(3*H*)-pyrimidone (2).

A mixture of 5-bromoisocytosine (7.90 g, 41.5 mmol), potassium carbonate (7.6 g, 55 mmol), 4-chlorothiophenol (8.0 g, 55 mmol), and *N,N*-dimethylformamide (56 ml) was heated to 110° under nitrogen atmosphere for 4 hours. The mixture was allowed to cool to ambient temperature, poured into ice (300 g), and neutralized with 1 *N* hydrochloric acid (~ 40 ml). The precipitate was filtered, and washed with cold water and ether until the solvent front running spot (disulfide) was not detected in the filtrate.This procedure resulted in 9.86 g (92%) of 2 as a colorless solid, mp 300-301°. ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 7.00 (br s, 2H, NH_2), 7.10 (d, 2H, ArH), 7.26 (d, 2H, ArH), 7.96 (s, 1H, ArH), 11.28 (br s, 1H, NH); ms (CI): m/z 254 (M+1, 100%), 256 (M+3, 45%), 282 (M+29, 20%).

*Anal.*Calcd. for $C_{10}H_8N_3OClS$: C, 47.34; H, 3.18; N, 16.56; Cl, 13.97; S, 12.64. Found: C, 47.08; H, 3.14; N, 16.37; Cl, 14.24; S, 12.44.

2-Amino-5-[(4-chlorophenyl)thio]-4-morpholinopyrimidine (4).

Method A. Thionyl chloride (15 ml, 24.5 g, 200 mmol) was added to *N,N*-dimethylformamide (15 ml, 14.16 g, 190 mmol) at 0° under a nitrogen atmosphere. The resulting solution was added slowly to a suspension of 2 (10.0 g, 39 mmol) in *N,N*-dimethylformamide (100 ml). After 15 minutes, hplc analysis of the reaction mixture showed a 92% conversion. The solvent was removed *in vacuo* at 45°. Ether was added and the hygroscopic yellow solid that precipitated was filtered and washed with copious amount of ether. The solid was kept under ether at all times to avoid contact with air. The suspension was transferred to a flask, evaporated to dryness, and dissolved in absolute ethanol (300 ml). Morpholine (35 ml, 34.86 g, 400 mol) was added slowly, and a precipitate appeared after 2.5 hours at ambient temperature. The mixture was filtered. The filtrate was concentrated, the residue redissolved in absolute ethanol (200 ml) and the resulting solution treated with 1 *M* sodium hydroxide in water (100 ml). After 1 hour at reflux, the solvent was evaporated and the residue was partitioned between water and methylene chloride. The organic phase was isolated, washed with water, dried (sodium sulfate), and concentrated. The resulting crude product was purified by flash chromatography [6] on silica gel with hexane/ethyl acetate (6:4) as the eluent to give 5.00 g (40%) of 4, mp 128-130° (lit mp 140-141° [8]). ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 3.46 (m, 4H, NCH_2), 3.70 (m, 4H, OCH_2), 6.77 (s, 2H, NH_2), 7.06 (d, 2H, ArH), 7.40 (d, 2H, ArH), 7.98 (s, 1H, H6); ms (CI): m/z 323 (M+1, 100%).

Anal. Calcd. for $C_{14}H_{15}N_4OClS$: C, 52.09; H, 4.68; N, 17.36; S, 9.93. Found: C, 52.33; H, 4.76; N, 17.30; S, 9.93.

Further elution of the column resulted in 0.44 g (4%) of 5, mp 164-166°; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 3.11 (s, 6H, $(CH_3)_2N$), 6.57 (s, 2H, NH_2), 7.04 (d, 2H, ArH), 7.38 (d, 2H, ArH), 7.91 (s, 1H, H6); ms (CI): m/z 281 (M+1, 100%), 309 (M+29, 19%).

Anal. Calcd. for $C_{12}H_{13}N_4ClS$: C, 51.42; H, 4.68; N, 20.00; S, 11.42; Cl, 12.48. Found: C, 51.39; H, 4.71; N, 19.95; S, 11.36; Cl, 12.56.

Method B [14]. Oxalyl chloride (51.5 ml, 75.0 g, 591 mmol) was added dropwise to a solution of 4-formylmorpholine (59.4 ml, 68.0 g, 591 mmol) in methylene chloride (600 ml) under a nitrogen atmosphere. Gas evolution stopped after 5 minutes at ambient temperature. After 30 minutes, a suspension of 3b (50.0 g, 197 mmol) in methylene chloride (300 ml) was added. The mixture was refluxed for 2 hours, poured into cold saturated aqueous sodium bicarbonate and stirred for 15 minutes. The organic layer was isolated, washed with saturated aqueous sodium bicarbonate, water, dried (sodium sulfate), and evaporated to give a crude yellowish solid (75.9 g). The solid was suspended in absolute ethanol (1000 ml) and morpholine (87.1 ml, 1 mol). After heating at reflux for 1 hour, 1 *M* sodium hydroxide (500 ml) was added, and the reflux was continued for 1 hour. The mixture was concentrated (~500 ml) and the residue was partitioned between water and methylene chloride. The organic phase was isolated, washed sequentially with water and brine, dried (sodium sulfate), and evaporated. Recrystallization from ethanol gave 46.9 g (74%) of 4 with spectral properties identical to those above.

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