Pergamon

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Tetrahedron Letters 44 (2003) 8361–8363

TETRAHEDRON LETTERS

Utility of 4,6-dichloro-2-(methylthio)-5-nitropyrimidine. Part 2: Solution phase synthesis of tetrasubstituted purines†

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Received 2 September 2003; revised 16 September 2003; accepted 16 September 2003

Abstract—A simple synthesis of tetrasubstituted purines is disclosed based on the solution phase elaboration of 4,6-dichloro-2-methylthio-5-nitropyrimidine. One-pot sequential C4 and C6 chloride substitution by secondary and primary amines yields 4,6-diamino-2-methylthio-5-nitropyrimidines. *m*CPBA-mediated oxidation of the methylthio moiety to the corresponding sulfone allows facile substitution at the 2-position. $CrCl_2$ assisted reduction of the nitro group, followed by acid catalyzed orthoester cyclization, then provides novel tetrasubstituted purines not accessible by other methods.

Due to an emerging general interest in synthetic purines as inhibitors of various biological processes,[2] a number of solution and solid-phase methodologies for their construction have recently been advanced.[3] As part of our own work in this area, we recently reported on the first example of a solid-phase methodology applicable to the regioselective synthesis of fully substituted purine libraries (Fig. 1).[1] In that paper, 4,6-dichloro-2-(methylthio)-5-nitropyrimidine[4] **1** was loaded onto resin by displacement at C-4, and then efficiently elaborated into a resin bound purine **2**. Cleavage from the resin was then conducted to provide purines **3**. Due to the linkage of the purine on the resin, a minor limitation of our solid-phase method is the inability to prepare compounds such as **4** (R^1, $R^7 \neq H$) containing a fully substituted amine at position 6. Herein, we disclose a simple solution phase method for the utilization of pyrimidine **1** in the synthesis of fully substituted purines **4**.

Our optimized procedure is exemplified in the synthesis of 9-isopropyl-8-methyl-6-*N*,*N*-methylbenzylamino-2-piperidinylpurine **7** according to the conditions set forth in Scheme 1. Reaction of **1** at room temperature with 1 equiv. of methylbenzylamine, followed after 20 min by treatment of the reaction mixture with 3 equiv. of isopropylamine for 3 h, provided intermediate **5**. Oxidation of the methylthio moiety to the sulfone was carried out with *m*CPBA, then piperidine was added to the crude reaction to effect a third displacement affording **6**. Finally, reduction of the nitro functionality according to the Miller[5] procedure was followed by acid catalyzed cyclization using trimethylorthoacetate to yield purine **7**. Analytically pure purine **7** was

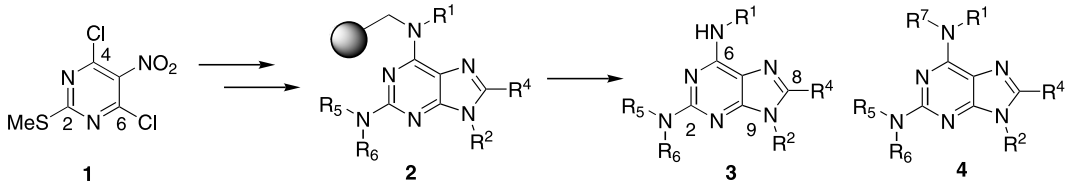

Figure 1. 2,6,8,9-Tetrasubstituted purines **3** and **4** accessible from the starting material 4,6-dichloro-(2-methylthio)-5-nitropyrimidine **1**.

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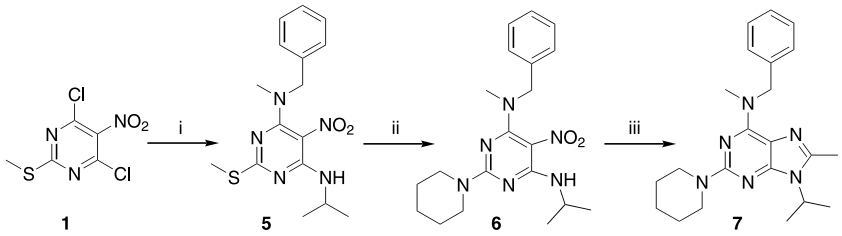
doi:10.1016/j.tetlet.2003.09.112



Scheme 1. Solution-phase synthesis of a 2,6,8,9-substituted purine. *Reagents and conditions*: (i) methylbenzylamine (1 equiv.), THF, Hunig's base, 20 min, rt, then; isopropylamine (3 equiv.), 3 h, rt; (ii) *m*CPBA, DCM, 16 h, rt, then; piperidine, 2 h, rt; (iii) $CrCl_2$ (10 equiv.), 20:1 DMF:MeOH, 4 h, rt, then; $MeC(OCH_3)_3$, $MeSO_3H$ (cat.), 24 h, 100°C.

obtained in an overall yield of 73% after recrystallization (see experimental section).

Noteworthy in this methodology is the ability to obtain final products **4** in high purity and good yield after a single purification at the end of the six-step three-pot sequence. This compares well with the overall efficiency of our nine-step solid-phase method, which can deliver final products **3** in good to excellent yield and purity after chromatography following cleavage from the solid support.[1] Further examples of fully substituted purines were prepared following our optimized procedure and are shown in Figure 2.[6] Note that even anilines can be utilized with our protocol, providing 9-aryl purines (**8**, **9**) difficult to obtain using other methods.

Our current solution-phase procedure requires the use of a secondary amine in one of the initial displacement steps in order to avoid a regiochemical complication in the purine formation step. As a result of this, products following this protocol are purines with fully substituted amines at position 6 (**4**, **7**–**10**). Our previously reported[1] solid-phase method requires the use of a primary amine in the initial reductive amination, thereby leading after cleavage to purines with a mono-substituted amine at position 6 (**3**). Thus these procedures are highly complimentary and allow ready access to all manner of fully substituted purines, representing a ready tool to those who wish to prepare them. A further manuscript describing an application to library synthesis is in progress.

Experimental

4,6-Dichloro-2-methylthio-5-nitropyrimidine (1). The starting material can be prepared according to the procedure of Harnden and Hurst or that of Brown and Jacobsen.[4]

4-(*N*,*N*-Benzylmethylamino)-6-(*N*-isopropylamino)-2-methylthio-5-nitropyrimidine (5). **1** (0.31 g; 1.29 mmol) was dissolved in THF and diisopropylethylamine (0.83 g; 6.46 mmol) was added. After stirring for 2 min, methylbenzylamine (0.16 g; 1.29 mmol) was added dropwise. The solution was allowed to stir for 20 min at room temperature after which 2-propylamine (0.23 g; 3.87 mmol) was added in one portion. The solution was stirred for an additional 3 h at room temperature. The THF was removed by rotary evaporation and the reaction crude distributed between diethyl ether and 10% NH_4Cl solution. The organic portion was washed with two additional portions 10% NH_4Cl solution and one portion saturated NaCl solution. The organic layer was dried over $MgSO_4$ and concentrated in vacuo to yield **5** as a yellow crystalline solid (0.44 g; 98% yield).

4-(*N*,*N*-Benzylmethylamino)-6-(*N*-isopropylamino)-5-nitro-2-piperidinylpyrimidine (6). **5** (0.44 g; 1.27 mmol) was dissolved in anhydrous dichloromethane and *m*-chloroperbenzoic acid (0.66 g; 77% max. purity, 2.94 mmol max.) was added in one portion. The reaction was stirred at room temperature for 16 h. The reaction was quenched with 2 mL piperidine and allowed to stir for an additional 2 h, after which the dichloromethane was removed in vacuo. The crude was dissolved in diethyl ether and washed with two portions 10% NH_4Cl solution, two portions saturated Na_2CO_3, and one portion saturated NaCl solution. The ether layer was dried over $MgSO_4$ and concentrated in vacuo to yield **6** as a yellow crystalline solid (0.43 g; 88% yield).

9-Isopropyl-8-methyl-6-*N*,*N*-methylbenzylamino-2-piperidinylpurine (7). **6** (0.43 g; 1.12 mmol) was dissolved in 20 mL 20:1 DMF:MeOH. Anhydrous $CrCl_2$ (1.40 g; 11.2 mmol) was added in one portion and the reaction allowed to stir at room temperature for 4 h. Trimethylortho-

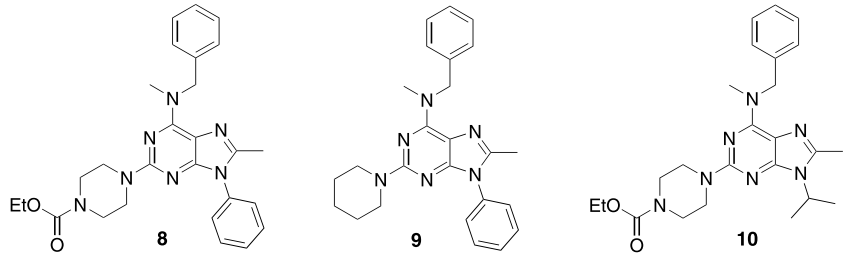


Figure 2. Additional examples of purines prepared by the present method.[6]

acetate (3 mL) was added to the reaction, followed by 4 drops of methane sulfonic acid, and the reaction was stirred at 100°C for 24 h. After cooling, the resulting solution was quenched with 200 mL water and extracted with three portions ethyl acetate. The combined ethyl acetate layers were washed with two portions 5% HCl, two portions $NaHCO_3$, one portion water and one portion saturated NaCl solution. The organic layer was dried over $MgSO_4$, and after filtration the solvents were removed in vacuo. The compound was then recrystallized from $MeOH/H_2O$ to yield **7** as a light yellow solid (0.36 g; 85%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.33–7.21 (m, 5H), 5.20 (s, 2H), 4.57 (m, 1H), 3.69 (dd, 4H), 3.31 (s, 3H), 2.42 (s, 3H), 1.59 (d, 6H), 1.57–1.44 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) 157.38, 154.12, 153.60, 144.14, 139.22, 128.76, 127.76, 127.22, 112.46, 52.56, 47.06, 45.29, 25.52, 24.91, 21.03, 14.84. MS (ESI) m/z calcd 378.25. Found: 379 $(M+H)^+$. Anal. calcd for $C_{22}H_{30}N_6$: C, 69.81; H, 7.99; N, 22.20. Found: C, 69.81; H, 7.94; N, 22.02. λ_{max} 297.0 nm, 245.5 nm. Mp: 130.9–132.6°C.

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6. These compounds gave ^1H NMR spectra consistent with their structures and showed purity >95% by LC/MS. Compound **8**, mp 114.1–116.2°C; compound **9**, oil; compound **10**, mp 120.4–121.5°C.