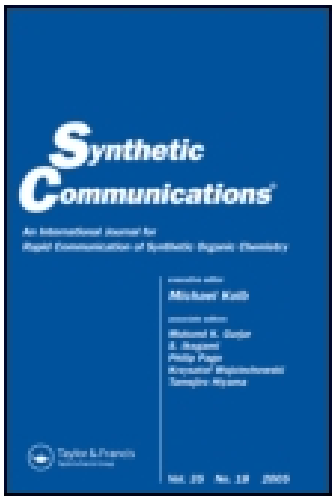

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 17 Aug 2006.

To cite this article: HeXi Chang , Carol Ensinger , Robert D. McCargar & Bruno M. Vittimberga (2003) Synthesis of an o-Nitrobenzyl Attached A_1 Adenosine Receptor Antagonist, a Prodrug Approach, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 33:15, 2605-2611, DOI: 10.1081/SCC-120021980

To link to this article: http://dx.doi.org/10.1081/SCC-120021980

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SYNTHETIC COMMUNICATIONS®
Vol. 33, No. 15, pp. 2605–2611, 2003

Synthesis of an *o*-Nitrobenzyl Attached A_1 Adenosine Receptor Antagonist, a Prodrug Approach

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ABSTRACT

The *o*-nitrobenzyl group, possessing distinct advantage of being photolabile under mild conditions, was successfully connected to 8-(5,6-epoxynorbornan-2-yl)-1,3-dipropylxanthine (**5**), a high specific A_1 adenosine receptor antagonist. The resulting compound **4** would have potential use as a prodrug.

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DOI: 10.1081/SCC-120021980 0039-7911 (Print); 1532-2432 (Online)

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Key Words: Photolysis; *o*-Nitrobenzyl group; A_1 adenosine receptor antagonist.

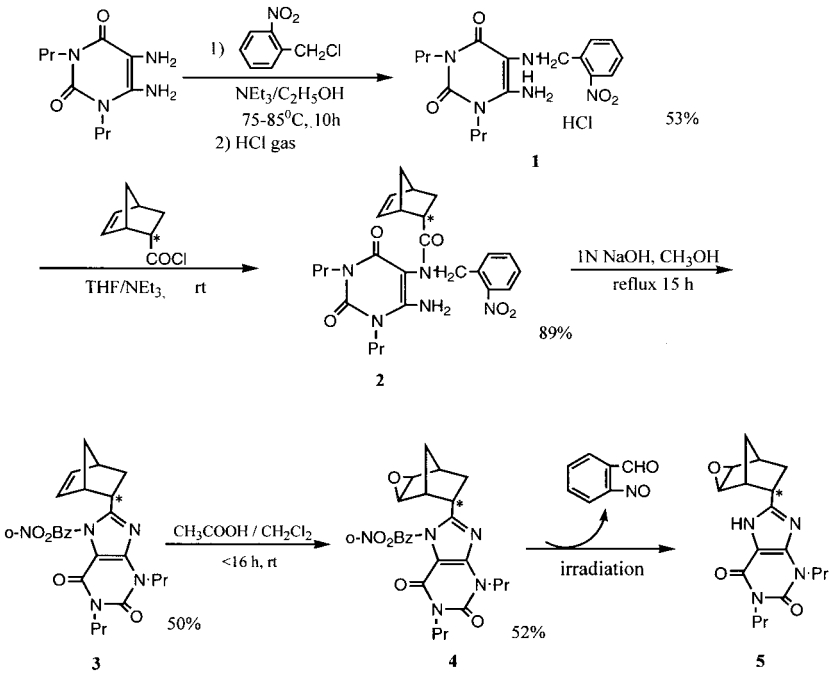
Since adenosine receptors were identified as drug targets,[1] a variety of xanthine derivatives have been prepared and biologically screened in order to find potent, receptor selective adenosine antagonists.[2] It is interesting to note that, 8-(5,6-epoxynorbornan-2-yl)-1,3-dipropylxanthine (**5**), a potential drug candidate for congestive heart failure, possesses high affinity and selectivity for the A_1 adenosine receptor.[3]

The *o*-Nitrobenzyl group, a special nitrogen protective group that is stable under most of conditions, can be cleaved by irradiation at 320 nm for 1 h in nearly quantitative yield.[4] This protective group has been used widely in a variety of structure syntheses.[5] It is important to mention that besides traditional photolytic conditions, removal of the *o*-nitrobenzyl group could also be carried out efficiently using direct sunlight.[6]

The use of different kinds of prodrugs have been an effective way to improve certain drug's absorption, distribution, as well as to achieve prolonged pharmaceutical effects by controlling drug-release.[7] Adding the *o*-nitrobenzyl group to the N-7 position of compound **5** could produce a compound (**4**) with some prodrug activity. By controlling exposure of **4** to sunlight, it is possible to release the drug gradually and therefore dramatically change its pharmaceutical properties.

A possible route to desired prodrug **4** could be the alkylation of 1,3-dipropyl-8-(5-norbornen-2-yl)xanthine[8] with *o*-nitrobenzyl bromide in the presence of a base (either NEt_3 or $NaNH_2$), and subsequent epoxidation of the norbornenyl double dond. But the chance to complete the alkylation reaction is little in considering of the high stereo-hindrance of norbornenyl ring and relative large *o*-nitrobenzyl group. The route that we eventually followed in preparing prodrug **4** is outlined in Sch. 1.

1,3-Dipropyl-5,6-diaminouracil, prepared according to the literature method,[9] was alkylated with *o*-nitrobenzyl chloride. The following acylation was then accomplished with (−)(1*S*,2*S*)-5-norborbene-2-carboxylic acid chloride yielding the corresponding amide **2**. Regarding this reaction, we found that when small quantities of reactants are used for the acylation, the order of reagents addition was not significant. Either adding compound **1** to the acid chloride or vice versa, will basically give the same results. However it is significant to note that when the reaction was scaled-up, only the addition of the acid chloride slowly to compound **1** produced the desired product in high yield as described in the Experimental section. The reverse addition will result



Scheme 1.

in the formation of a di-acylated side product due to the presence of excess amount of acid chloride.

The amide **2** underwent ring closure when it was heated at reflux in basic alcohol solution to form the xanthine derivative **3**. This compound was then subjected to epoxidation with peracetic acid to give the expected prodrug **4**. Other epoxidation reagents that were tried include magnesium monoperoxyphthalate hexahydrate (MMPP) and urea hydrogen peroxide, but unlike peracetic acid, both of these cannot drive the reaction to completion.

Photolytic deprotection of **4** was carried out by irradiating a solution of **4** in either THF or *sec*-BuOH with a 450 W UV lamp for 3–6 h. Under these reaction conditions no racemization was observed, which was further confirmed by measuring the HPLC chiral purity of product **5** obtained.

In conclusion, an *o*-nitrobenzyl attached A_1 adenosine receptor antagonist **4** has been prepared. The target compound **4** has potential as a prodrug and further pharmaceutical related activities are currently under investigation.

EXPERIMENTAL

Melting points were determined on an Electrothermal Digital Melting Point Apparatus (IA9300). ^{1}H-NMR spectra were measured on a Bruker spectrometer (400 MHz). Elemental analysis was performed by QTI, Whitehouse, NJ. HPLC analyses were performed on an Alliance Waters 2690 Separations Module system with Waters 996 Photodiode Array Detector. The chemical purity was measured by reversed-phase HPLC using a Keystone BDS Hypersil C8 column (150 × 2.0 mm, 5 μm). The chiral purity was measured by normal phase HPLC using a Chiralcel OD column (250 × 4.6 mm, 10 μm).

6-Amino-1,3-dipropyl-5-(*o*-nitrobenzyl)aminouracil HCl salt (1). To the mixture of 1,3-dipropyl-5,6-diaminouracil (24 g, 0.1 mmol), *o*-nitrobenzyl chloride (20 g, 0.12 mol) in ethanol (400 mL) was added triethyl amine (16 g, 0.16 mol). The mixture was heated at reflux in an oil bath for 12 h. After removing the solvents in vacuo, water (300 mL) was added to the residue. The mixture was extracted with ethyl acetate (2 × 150 mL) and the organic layer was dried with $MgSO_4$. After removing the solvent under vacuum, THF (30 mL) was added to the residue and the mixture was cooled in an ice bath. Then HCl gas was passed through the solution to the saturation point and the resultant suspension was stirred with cooling for 1 h. The solid was filtered and washed with THF to give product **1** as yellow solid (27.8 g, 67% yield); m.p. 193.8–194.9°C. ^{1}H-NMR (DMSO): (ppm) 7.80–7.30 (m, 4H, Ph-H), 4.30 (s, 2H, N-CH_2-Ph), 3.53 (t, 2H, N-CH_2-C), 3.41 (t, 2H, N-CH_2-C), 1.25 (m, 2H, C-CH_2-C), 1.15 (m, 2H, C-CH_2-C), 0.65 (t, 3H, CH_3), 0.55 (t, 3H, CH_3).

Analysis: $C_{17}H_{24}ClN_5O_4$: Calcd. C, 51.32; H, 6.04; N, 17.61.

Found: C, 51.73; H, 6.09; N, 17.24.

6-Amino-1,3-dipropyl-5-{[(1*S*,2*S*)-5-norbornen-2-yl-acyl]-(*o*-nitrobenzyl)}aminouracil (2). To the solution of (−)(1*S*,2*S*)-5-norborbene-2-carboxylic acid[10] (5 g, 36 mmol) in CH_2Cl_2 (125 mL), was added dropwise diluted oxalyl chloride (5 mL in 125 mL CH_2Cl_2). After stirring at r.t. for 2 h, the mixture was concentrated under vacuum and then 200 mL of CH_2Cl_2 was added to the residue. The resultant solution was concentrated again as before and the residue was dissolved in 125 mL of THF. In a separate flask, a slurry of diamine salt (**1**) (12.75 g, 32 mmol), triethyl amine (11 g, 110 mmol) in THF (250 mL) was stirred at r.t. for 2 h. The mixture was then cooled with an ice bath and the acid chloride solution in THF prepared above was added dropwise. The resultant yellow suspension was stirred overnight. The mixture was then diluted with water (1500 mL) and stirred for an additional 3 h. The product was isolated

by filtration as a yellow solid, washed with water, and air dried (14.5 g, 94% yield); m.p. 186.8–189.2°C.

Analysis: $C_{25}H_{31}N_5O_5$: Calcd. C, 62.37; H, 6.44; N, 14.55.

Found: C, 62.00; H, 6.45; N, 14.68.

1,3-Dipropyl-7-*o*-nitrobenzyl-8-[(1*S*,2*S*)-5-norbornen-2-yl]xanthine (3). To the suspension of compound **2** (33.5 g, 70 mmol) in MeOH (300 mL) was added aqueous NaOH (1N, 300 mL). The mixture was refluxed for 15 h, followed by adding 600 mL of water. The resulting mixture was cooled in an ice bath and stirred for an additional 2 h. Product **3** was isolated by filtration as a light yellow solid (14 g, 43% yield); m.p 134.9–138.1°C; 97.58% HPLC chemical purity. ^{1}H-NMR ($CDCl_3$): (ppm) 8.23 (d, 1H, Ph-H), 7.55 (t, 1H, Ph-H), 7.47 (t, 1H, Ph-H), 6.59 (d, 1H, Ph-H), 6.20 (dd, 1H, C_6H), 6.00 (s, 2H, N-CH_2-Ph), 5.80 (dd, 1H, C_5H), 4.05 (t, 2H, N-CH_2-C), 3.83 (t, 2H, N-CH_2-C), 3.17 (dt, 1H, C_2H), 3.00 (s, 1H, C_1H), 2.92 (s, 1H, C_4H), 2.02 (m, 1H, $C_{3a}H$), 1.79 (m, 2H, C-CH_2-C), 1.70–1.48 (m, 3H, $C_{3b}H$ + C-CH_2-C), 1.45 (d, 1H, $C_{7a}H$), 1.30 (d, 1H, $C_{7b}H$), 0.97 (t, 3H, CH_3), 0.87 (t, 3H, CH_3).

Analysis: $C_{25}H_{29}N_5O_4$: Calcd. C, 64.79; H, 6.26; N, 15.12.

Found: C, 64.56; H, 6.29; N, 15.03.

1,3-Dipropyl-7-*o*-nitrobenzyl-8-[5,6-*exo*-epoxy-(1*S*,2*S*)-norbornan-2-yl]xanthine (4). To a solution of compound **3** (4 g, 8.65 mmol) in CH_2Cl_2 (100 mL) was added peracetic acid (32% Wt., 8.4 g, 35.37 mmol). The clear, light yellow solution was stirred at r.t. for 16 h, and then saturated aqueous $NaHCO_3$ (20 mL) was added. The organic layer was separated and washed with saturated $NaHCO_3$ (100 mL), $Na_2S_2O_3$ (1M, 100 mL), water (100 mL), and then dried over Na_2SO_4. After removing solvent, ether (15 mL) was added to the residue and the mixture was stirred at r.t. for half an hour. The product was obtained as a white solid by filtration (1.8 g, 44% yield); m.p. 181.4–183.6°C; 99.42% HPLC chemical purity. ^{1}H-NMR ($CDCl_3$): (ppm) 8.22 (d, 1H, Ph-H), 7.57 (t, 1H, Ph-H), 7.48 (t, 1H, Ph-H), 6.59 (d, 1H, Ph-H), 5.97 (s, 2H, N-CH_2-Ph), 4.08 (t, 2H, N-CH_2-C), 3.87 (t, 2H, N-CH_2-C), 3.26 (s, 2H, C_5H + C_6H), 3.08 (dt, 1H, C_2H), 2.60 (s, 1H, C_1H), 2.52 (s, 1H, C_4H), 1.90 (m, 2H, C_3H), 1.80 (m, 2H, C-CH_2-C), 1.70–1.51 (m, 3H, $C_{7a}H$ + C-CH_2-C), 1.48 (d, 1H, $C_{7b}H$), 0.97 (t, 3H, CH_3), 0.89 (t, 3H, CH_3).

Analysis: $C_{25}H_{29}N_5O_5$: Calcd. C, 62.63; H, 6.05; N, 14.61.

Found: C, 62.68; H, 6.01; N, 14.54.

1,3-Dipropyl-8-[5,6-*exo*-epoxy-(1*S*,2*S*)-norbornan-2-yl]xanthine (5). A solution of **4** (200 mg, 0.42 mmol) in 10 mL of THF or *sec*-BuOH was deaerated with nitrogen for 10 min in a Pyrex testing tube. The solution was irradiated for 6 h at 45–50°C with a 450-W Hanovia photochemical lamp. The resulting solution was concentrated in vacuo to a brown oil,

which was then dissolved in ethyl acetate (10 mL) and filtered through a silica gel pad. The filtrate was washed with water (10 mL) and dried with Na_2SO_4. After removing solvent under vacuum, the residue was stirred with hexane (5 mL) at r.t. for half an hour. The de-protected product **5** was collected by filtration as an off-white solid (76 mg, 53% yield); m.p. 135.0–138.5°C; 95.02% HPLC chemical purity; 100% HPLC chiral purity. ^{1}H-NMR ($CDCl_3$): (ppm) 4.09 (t, 2H, N-CH_2-C), 3.98 (t, 2H, N-CH_2-C), 3.42 (dt, 1H, C_2H), 3.23 (d, 1H, C_6H), 3.10 (d, 1H, C_5H), 3.05 (s, 1H, C_1H), 2.65 (s, 1H, C_4H), 2.04 (m, 2H, C_3H), 1.90–1.60 (m, 5H, 2C-CH_2-C + $C_{7a}H$), 1.54 (d, 1H, $C_{7b}H$), 0.99 (t, 3H, CH_3), 0.94 (t, 3H, CH_3).

Analysis: $C_{25}H_{29}N_5O_5$: Calcd. C, 62.72; H, 6.97; N, 16.26.
Found: C, 62.91; H, 6.91; N, 16.13.

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Received in Japan September 21, 2002

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