Pergamon

Tetrahedron Letters, Vol. 37, No. 10, pp. 1567-1570, 1996

0040-4039/96 $15.00 + 0.00

S0040-4039(96)00092-5

An Improved Approach to the Synthesis of Adenosine-5'-N-Ethyluronamides of Interest as Adenosine Receptor Agonists

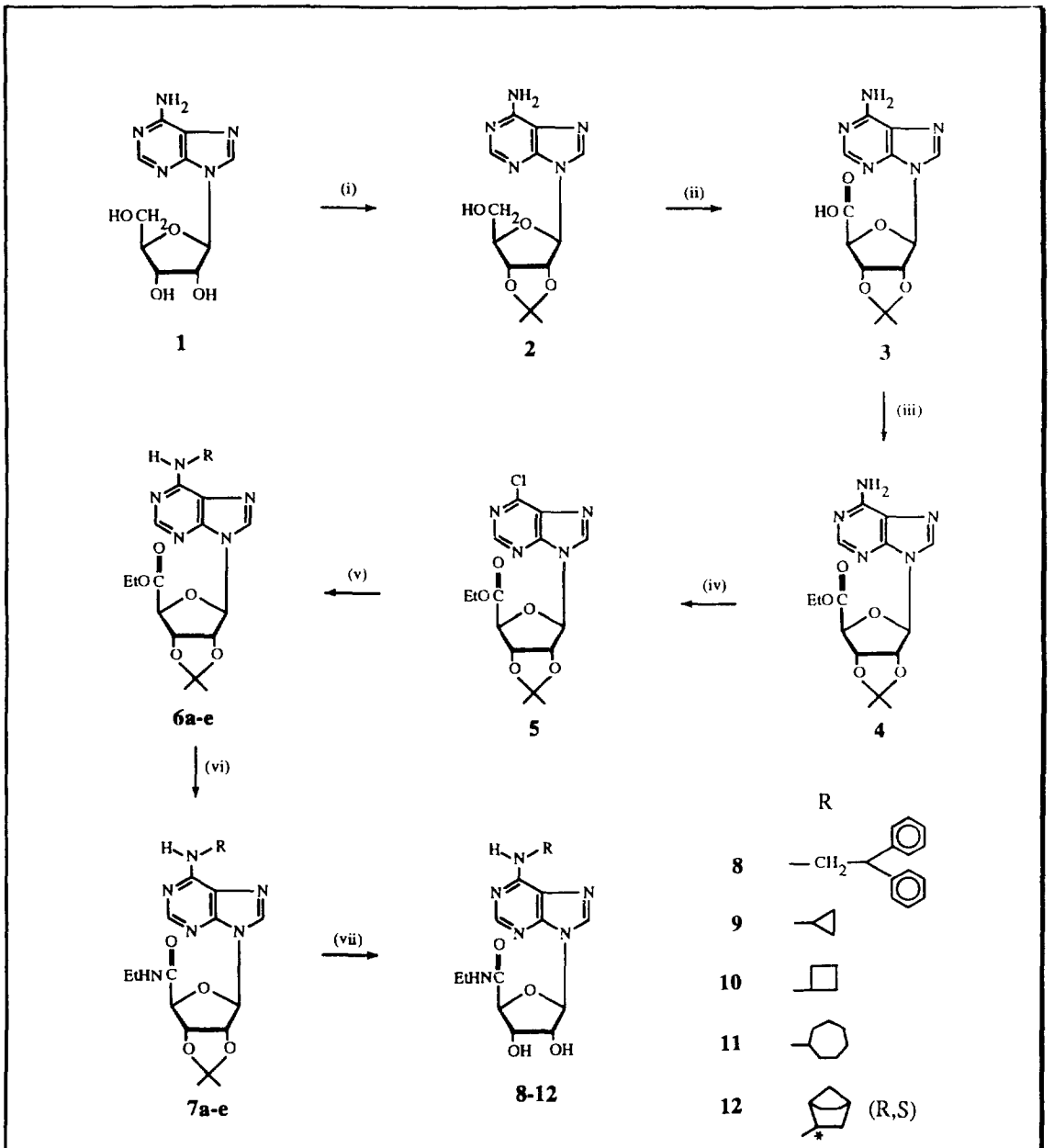
Seung B. Ha and Vasu Nair*

Department of Chemistry, The University of Iowa, Iowa City, Iowa 52242

Abstract: Adenosine-5'-N-ethyluronamides which are modified at the 6-amino group are of considerable interest as adenosine receptor agonists. This report describes a new and efficient approach to the synthesis of this class of biologically active compounds.

The natural nucleoside, adenosine, exerts its physiological effects *via* extracellular adenosine receptors, termed A_1, A_2, A_3, which are distributed throughout a wide variety of tissues in mammalian systems.[1-3] Adenosine has been clinically approved as a medication by the FDA for the treatment of supraventricular tachycardia.[4] However, adenosine therapeutics is limited by its rapid metabolic inactivation and non-selectivity for the receptor subtypes.[5] There has been considerable interest in developing adenosine receptor agonists that have metabolic stability and high A_1, A_2, or A_3 receptor binding affinity and selectivity.[5] Several adenosine-5'-N-ethyluronamide derivatives have recently been discovered as potent adenosine A_1, A_2, or A_3 receptor agonists.[6-8] For example, N^6-cyclopentyladenosine-5'-N-ethyluronamide shows potent A_1 agonist activity (K_i = 0.50 nM) with a selectivity ratio, A_2/A_1 = 270,[6] while N^6-benzyladenosine-5'-N-ethyluronamide exhibits strong A_3 receptor binding (K_i = 6.8 nM) with A_1/A_3 and A_2/A_3 ratios of 14.[8] The majority of these compounds have been synthesized by the methodology of Olsson and coworkers which uses inosine as the starting material.[6] However, oxidation of the isopropylidene protected inosine to the corresponding 5'-carboxylic acid with CrO_3/acetic acid is problematic and only moderate yields of product are obtained. We have also found that a double chlorination to form the key intermediate, 2',3'-O-isopropylidene-6-chloropurine-5'-carboxylic acid chloride from the corresponding inosine-5'-carboxylic acid is not favorable under the reported reaction conditions. Another known methodology for the synthesis of N^6-substituted adenosine-5'-N-ethyluronamides utilizes the Dimroth rearrangement of N^1-alkylated 5'-N-ethyluronamidoadenosine.[8] However, this approach has serious limitations; only methyl, benzyl, or allylic halides can alkylate the N^1 of adenosine derivatives to an extent that is synthetically useful. This paper reports on a new approach to the synthesis of N^6-substituted adenosine-5'-N-ethyluronamides of interest as adenosine A_1 or A_2 receptor agonists. The pathway used is general and reproducible and the overall yields using this approach are higher compared to previous methods.

Adenosine (**1**) was used as the starting material in the synthesis of N^6-substituted adenosine-5'-N-ethyluronamide analogues (**8-12**). It was protected as its 2',3'-O-acetonide[9] by reaction with 2,2- dimethoxy-



(i) acetone,TsOH,$(CH_3)_2C(OCH_3)_2$; (ii) $KMnO_4$,KOH; (iii) $SOCl_2$,EtOH; (iv) *n*-$C_5H_{11}ONO$,CCl_4,CH_3CN; (v) aralkyl or cycloalkylamine,Et_3N, CH_3CN; (vi) $EtNH_2$.HCl,Et_3N,CH_3CN; (vii) 1N HCl

Scheme 1

propane and *p*-toluenesulfonic acid in acetone at room temperature for 1 h (Scheme 1). The 5'-hydroxyl group of the 2',3'-O-acetonide **2** was oxidized to the carboxylic acid under conditions of high dilution[10] with excess of $KMnO_4$ (3 molar equivalents) in a KOH solution adjusted to pH 12.5. This oxidation reaction which involved stirring the reaction mixture at room temperature for 24 h gave consistently high yields of the 5'-uronic acid (> 86%). Conversion of the carboxylic acid **3**[11] to the ethyl ester **4**[12] (82 % yield) was accomplished by stirring the nucleoside in absolute ethanol under N_2 and slowly dripping in an equimolar amount of thionyl chloride at 0 °C, and then stirring the reaction mixture at room temperature for 18 h.[6] Activation of the 5'-carboxylic acid as its ethyl ester for the eventual uronamide formation also allowed the use of a thermally-induced radical deamination-halogenation reaction to form the 6-chloropurine riboside analogue **5**.[13-15] The radical reaction was accomplished at 60 °C under N_2 with *n*-pentyl nitrite as the aprotic diazotization agent, CCl_4 as the chlorine atom donor, and acetonitrile as the solvent to afford compound **5**[16] in 70 % purified yield. The 6-chloro group of **5** was displaced by the appropriate aralkyl or cycloalkylamine in acetonitrile in the presence of triethylamine at room temperature to give the N^6-substituted adenosine-5'-carboxylic acid ethyl ester derivatives **6a-e** (75-90 % yield).[17] The ethyl esters **6a-e** were converted to the corresponding ethyluronamides **7a-e** in 60-70 % yield by stirring in a closed system with an excess of ethylamine hydrochloride and triethylamine in acetonitrile at 55 °C for 48 h. Compounds **7a-e** were easily deprotected with 1N HCl at 55 °C for 3 h to provide target compounds **8-12** (Scheme 1).[18]

In summary, a new and efficient approach to the synthesis of N^6-aralkyl or N^6-cycloalkyladenosine-5'-N-ethyluronamides of interest as adenosine receptor agonists has been developed. The methodology is general and can be used for the synthesis of a wide variety of new or known N^6-substituted adenosine uronamides. The new target compounds presented as examples are related to known potent adenosine A_1, A_2, or A_3 receptor agonists. As a result of substitution at the N^6-position and particularly because of the alteration of the 5'-CH_2OH, these compounds are metabolically stable with respect to hydrolytic deamination by adenosine deaminase.

Acknowledgment. Support of this research by the National Institutes of Health is gratefully acknowledged.

References and Notes.

1. Londos, C.; Wolff, J. *Proc. Natl. Acad. Sci. U.S.A.* **1977**, *74*, 5482-5486.
2. Muller, C. E.; Scior, T. *Pharm. Acta. Helv.* **1993**, *68*, 77-111.
3. *Adenosine and Adenosine Receptors*; Williams, M., Ed.; Humana Publishing: Clifton, New Jersey, 1990; pp 1-17.
4. Pantely, G. A.; Bristow, J. D. *Circulation* **1990**, *82*, 1854-1856.
5. Jacobson, K. A.; van Galen, P. J. M.; Williams, M. *J. Med. Chem.* **1992**, *35*, 407-422.
6. Olsson, R. A.; Kusachi, S.; Thompson, R. D.; Ukena, D.; Padgett, W.; Daly, J. W. *J. Med. Chem.* **1986**, *29*, 1683-1689.

7. Bridges, A. J.; Bruns, R. F.; Ortwine, D. F.; Priebe, S. R.; Szotek, D. L.; Trivedi, B. K. *J. Med. Chem.* **1988**, *31*, 1282-1285.
8. Gallo-Rodriguez, C.; Ji, X. D.; Melman, N.; Siegman, B. D.; Sanders, L. H.; Orlina, J.; Fischer, B.; Pu, Q.; Olah, M. E.; van Galen, P. J. M.; Stiles, G. L.; Jacobson, K. A. *J. Med. Chem.* **1994**, *37*, 636-646.
9. Hampton, A. *J. Am. Chem. Soc.* **1961**, *83*, 3640-3645.
10. Hutchison, A. J.; Williams, M.; de Jesus, R.; Yokoyama, R.; Oei, H. H.; Ghai, G. R.; Webb, R. L.; Zoganas, H. C.; Stone, G. A.; Jarvis, M. F. *J. Med. Chem.* **1990**, *33*, 1919-1924.
11. Preparation of **3**: To a stirred mixture of **2** (4.00 g, 13 mmol) and a solution of KOH (2.19 g, 39 mmol) in water (600 mL) was added $KMnO_4$ (6.17 g, 39 mmol) in water (300 mL). The reaction mixture was vigorously stirred at room temperature for 24 h. The reaction was quenched by addition of 7.5 % aqueous H_2O_2 solution (150 mL) and the mixture was filtered through Celite, concentrated *in vacuo* to about 75 mL, and acidified to pH 4 with 3N HCl. The precipitated product was collected and dried *in vacuo* to give 3.61 g (86 %) of **3**[6] as a white solid: mp 274-276 °C; UV (H_2O) λ_{max} 257 nm; ^{1}H NMR (DMSO-d_6) δ 1.35 (s, 3H), 1.52 (s, 3H), 4.67 (s, 1H), 5.50 (m, 2H), 6.32 (s, 1H), 7.26 (br s, 2H), 8.08 (s, 1H), 8.26 (s, 1H).
12. Preparation of **4**: A suspension of **3** (3.63 g, 11 mmol) in absolute EtOH was cooled to 0 °C with stirring. Thionyl chloride (0.82 mL, 11 mmol) was dripped in slowly and the mixture was allowed to stir at room temperature for 18 h under N_2. The solvent was evaporated and the residue was purified by flash column chromatography on silica gel to afford 3.23 g (82 %) of **4**[6] as a yellow oil: ^{1}H NMR (DMSO-d_6) δ 0.92 (t, 3H), 1.35 (s, 3H), 1.52 (s, 3H), 3.77 (m, 2H), 4.86 (s, 1H), 5.51 (m, 2H), 6.43 (s, 1H), 8.24 (br s, 2H), 8.30 (s, 1H), 8.46 (s, 1H).
13. Nair, V.; Richardson, S. G. *J. Org. Chem.* **1980**, *45*, 3969-3974.
14. Nair, V.; Richardson, S. G. *Synthesis* **1982**, 670-672.
15. Nair, V.; Fasbender, A. J. *Tetrahedron* **1993**, *49*, 2169-2184.
16. Preparation of **5**: To a solution of **4** (2.11 g, 6 mmol) in CCl_4 (40 mL) and acetonitrile (50 mL) was added *n*-pentyl nitrite (1.60 mL, 12 mmol) in an ice/water bath under N_2. The reaction mixture was stirred at 60 °C overnight. Evaporation of the solvent and purification of the resulting residue by flash column chromatography on silica gel gave 1.55 g (70 %) of **5** as a yellow oil: UV (MeOH) λ_{max} 263 nm; ^{1}H NMR (DMSO-d_6) δ 1.03 (t, 3H), 1.43 (s, 3H), 1.62 (s, 3H), 3.87 (m, 2H), 4.85 (s, 1H), 5.56 (m, 2H), 6.29 (s, 1H), 8.32 (s, 1H), 8.67 (s, 1H).
17. General procedure for the preparation of **6a-e**: To a solution of **5** in CH_3CN was added the appropriate amine (1.5 eq) and Et_3N (1.2 eq) under N_2. The reaction mixture was stirred at room temperature for 12 h. The solvent was removed under reduced pressure and the product was purified by flash column chromatography on silica gel.
18. Physical data for N^6-(2,2-diphenylethyl)adenosine-5'-N-ethyluronamide (**8**): mp 124-126 °C; IR (carbonyl) 1653 cm^{-1}; UV (MeOH) λ_{max} 267 nm (ε 19,360); ^{1}H NMR (DMSO-d_6) δ 1.09 (t, 3H), 3.25 (q, 2H), 4.15 (m, 3H), 4.31 (m, 1H), 4.61 (m, 2H), 5.48-5.87 (br m, 2H), 5.95 (d, 1H), 7.10-7.43 (m, 10H), 7.95 (br m, 1H), 8.36 (s, 2H), 8.88 (t, 1H); ^{13}C NMR (DMSO-d_6) δ 14.55, 33.05, 43.95, 49.34, 71.83, 72.92, 84.44, 87.56, 119.7, 126.1, 127.8, 128.2, 140.3, 142.6, 147.8, 152.2, 154.3, 168.9.
Anal. Calcd for $C_{26}H_{28}N_6O_4$: C, 63.93; H, 5.78; N, 17.20. Found: C, 63.56; H, 5.54; N, 16.74.

(*Received in USA* 12 *October* 1995; *revised* 19 *December* 1995; *accepted* 3 *January* 1996)