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Synthesis of Complex Ethynyladenosines Using Organic Triflic Enolates in Palladium-Catalyzed Reactions: Potential Agonists for the Adenosine A_2 Receptor

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Abstract: Many high affinity adenosine A_2 receptor agonists contain substituents at position 2 of the purine base. In the search for new methodology to develop C-2 substituted adenosine analogues, we have applied organic triflates in palladium-catalyzed cross-couplings that resulted in new 2-cycloalkylated ethynyl-adenosines. The organic triflates are derived from commercially available ketones and, when used in the cross-couplings, result generally in clean reactions with good yields. These are the first examples of the utilization of organic triflates in palladium-catalyzed cross-coupling reactions in the synthesis of modified nucleosides.

Introduction

The adenosine receptors, G-protein coupled receptors with high affinity for the natural nucleoside adenosine (**1**), have been of considerable interest because of their potential for pharmaceutical applications. Adenosine, unfortunately, is a metabolically unstable natural molecule and is converted rapidly by the ubiquitous enzyme, adenosine deaminase, to inosine. Its utility for most pharmaceutical applications is therefore limited. Considerable effort has been extended toward the development of adenosine analogues that

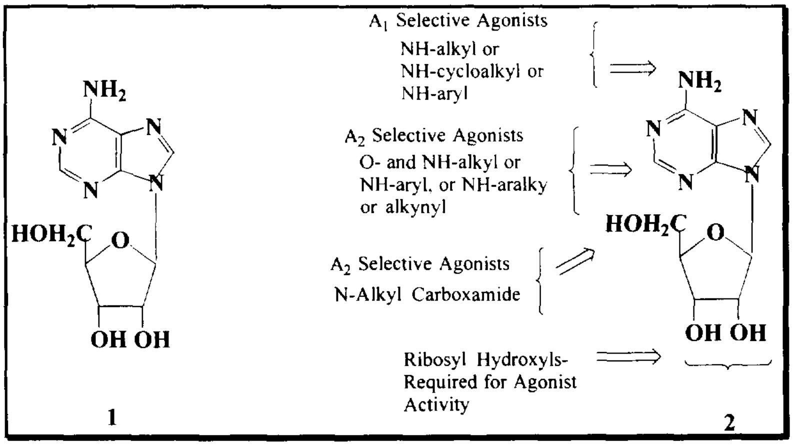


Figure 1

exhibit high receptor affinity and metabolic stability. There have been three adenosine receptor subtypes isolated and termed A_1, A_2, and A_3.[1-4] While substrates for the A_1 and A_3 receptors are primarily modified at the N^6 position of adenosine, those that are A_2 substrates involve modification at C-2 of the purine base including alkynyl type substitution (**2**, Figure 1).[5-9] While the selectivity ratios of the latter compounds are of the order of 10, it is clear that interesting leads for A_2 agonist activity have been discovered. However, before this discovery can be exploited to produce A_2 agonists with greater selectivity, new synthetic methodologies for the introduction of extended unsaturation at the 2-position of the adenine ring must be found, because the development of new A_2 receptor agonists has been hampered by limitations in synthetic methodology. This paper reports on the use of triflic enolates in a new application of palladium-mediated coupling reactions in nucleoside chemistry, the introduction of extended unsaturation at the 2-position of the adenine moiety of adenosine.

One of the best synthetic methodologies available for the formation of carbon-carbon bonds at the C-2 position of the purine ring is the palladium-catalyzed cross-coupling reaction.[10-16] This methodology is useful for nucleosides because it is clean, high yielding, and tolerant of other functional groups that may be present.[11] Palladium-catalyzed cross-couplings have been found to occur with a variety of organometallic and related reagents including organostannane, organozinc, organoaluminum, and organoboron reagents. Recently, organotriflates have been found to undergo palladium-mediated cross-coupling reactions.[17,18] In the continued development of synthetic approaches to novel adenosine agonists, we have carried out the first applications in nucleoside chemistry of palladium-catalyzed cross-couplings with organic triflates.[19]

Results and Discussion

The key feature to the synthetic development of these compounds is the application, twice, of the palladium (0) catalyzed cross-coupling reaction (Figure 2). Conversion of 2-iodoadenosine to 2-ethynyladenosine is the result of the first cross-coupling reaction. The second palladium-mediated reaction occurs with an organic triflate and 2-ethynyladenosine. This step is similar to the first palladium-catalyzed reaction but with the addition of LiCl. Stille proposed that the addition of LiCl was necessary for a vinyl palladium chloride complex to occur to insure transmetalation.[20]

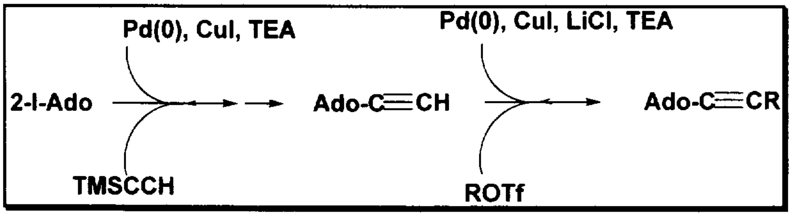
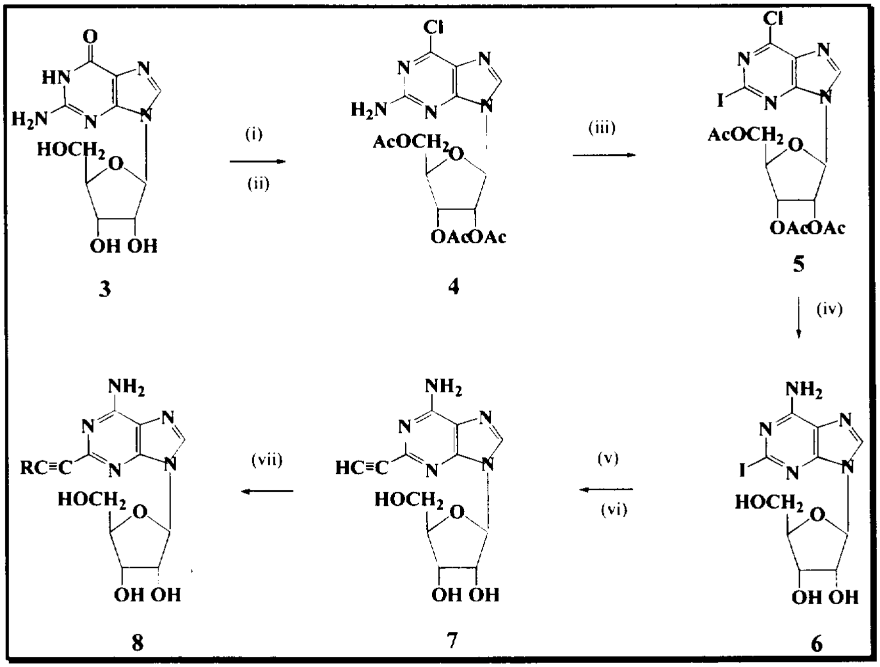


Figure 2

The starting compound for the synthesis was natural guanosine which was converted to 2-iodoadenosine as follows. Guanosine (**3**) was first acetylated with acetic anhydride and 4-dimethylaminopyridine in quantitative yields (Scheme 1). The acetylated product was then converted to its masked 6-chloro form (**4**) with phosphorous oxychloride. While this is a well-known reaction,[21] we have repeatedly found that even in the multigram scale reaction, care must be taken to limit reaction times to 1 hour or less since longer times result in considerable charring. The 2-iodo-6-chloropurine riboside triacetate (**5**) was formed from the 2-amino derivative by the use of a radical deamination-halogenation procedure.[10,11] Deprotection of the ribosyl hydroxyl groups and displacement of the 6-chloro substituent can be carried out simultaneously by treatment of **5** with ammonia in a chilled methanol solution.[22] The resulting 2-iodoadenosine (**6**) was isolated as a light yellow solid following purification by silica gel column chromatography.



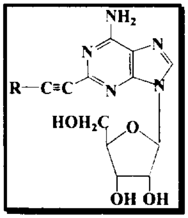
Reagents: (i) Ac_2O, TEA, DMAP, CH_3CN, 25 °C; (ii) $POCl_3$, N,N-diethylaniline, 60 °C;
(iii) CH_2I_2, n-$C_5H_{11}ONO$, CH_3CN, 65 °C; (iv) NH_3, CH_3OH, 0-25 °C;
(v) $Pd(Ph_3P)_4$, CuI, TMSCCH, TEA, DMF, 80 °C; (vi) ET_4NF, CH_3CN, 25 °C;
(vii) $Pd(Ph_3P)_4$, CuI, LiCl, ROTf, TEA, DMF, 80 °C.

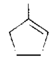
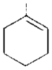
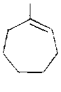
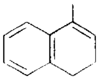
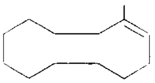
Scheme 1

The first of the two palladium (0) catalyzed cross-couplings was performed with 2-iodoadenosine, trimethylsilylacetylene, CuI, triethylamine, and tetrakis-(triphenylphosphine) palladium (0) in DMF at 80 °C for

70 minutes (Scheme 1).[16,23] This reaction has been carried out repeatedly in our laboratory and has proven to be clean and high yielding. Product formation can be followed by TLC (10 % MeOH/$CHCl_3$) and by the change in the UV spectrum from λ_{max} 264 nm for 2-iodoadenosine to λ_{max} 262 nm plus a significant shoulder at 286 nm for the immediate product. Conversion of the isolated 2-trimethylsilylethynyladenosine to 2-ethynyl-adenosine (7) was carried out with Et_4NF in acetonitrile. The overall yield for these two steps was 64 %. The second cross-coupling reaction which involved the transformation of 7 to 2-(2-cycloalkenylethynyl)-adenosine (8) utilized CuI, triethylamine, LiCl, tetrakis(triphenylphosphine) palladium (0) and the appropriate organic triflate. Organic triflates were prepared in good yields from available cyclic ketones by a procedure described by Stang and Dueber.[24] The organic triflate was introduced into the reaction mixture immediately before heating. As with the first cross-coupling, the almost instantaneous formation of palladium black

Table 1. Isolated Yields of Representative 2-(2-Cycloalkenylethynyl)adenosine Formed in Pd(0) Mediated Reactions with Triflic Enolates



R	mp (°C)	Yield
	157-159	54%
	119-120	87%
	132-134	23%
	120-123	55%
	156-158	61%

indicates rapid product formation. Completion of the reaction could be monitored by changes in the TLC plates (10 % MeOH/$CHCl_3$, R_f of product ≅ 0.4), and also by a major change in the UV spectrum from λ_{max} 264, 286 nm (sh) to λ_{max} 296 nm, 310 nm (sh). The final products were isolated using silica gel chromatography (10 % MeOH/$CHCl_3$) and purified by reversed-phase HPLC using Amberlite XAD-4 resin with gradient elution (EtOH/H_2O) (see Table 1 for yields).

In summary, synthetic approaches to a number of novel C-2 substituted adenosine analogues with potential A_2 agonist affinity have been developed through the use of organic triflates in palladium-catalyzed cross-coupling reactions. This is the first application of organic triflates in palladium catalyzed cross-coupling reactions in the synthesis of modified nucleosides. Given the number of commercially available ketones, numerous novel 2-(2-substituted ethynyl)adenosine analogues could be easily produced by this method.

Experimental Section

All chemicals were purchased from Aldrich or Sigma Chemical Companies. Solvents were distilled before use according to standard methods. Melting points reported are uncorrected and were determined on a Thomas-Hoover melting point apparatus fitted with a microscope. Nuclear magnetic resonance spectra were recorded on a Bruker Model AC300 pulse Fourier transform spectrometer. Ultraviolet spectra were recorded on a Gilford Response spectrophotometer. Chromatography was carried out using glass columns packed with 63-200 mesh silica gel. High performance liquid chromatography was done at 100 psi using Altex columns packed with 40-60 microns Amberlite XAD-4 resin (40-60 microns). Fractions were monitored by a Pharmacia UV-2 ultraviolet monitor and products were collected on a Gilson FC-100 fraction collector.

2-Iodoadenosine: This compound was prepared in four steps from guanosineas previously described by us.[22] It was obtained as an off-white solid: mp 142-144 °C; ^1H NMR (Me_2SO-d_6) δ 3.65 (m, 2H), 3.93 (q, 1H), 4.11 (q, 1H), 4.51 (q, 1H), 5.04 (t, 1H), 5.21 (d, 1H), 5.46 (d, 1H), 5.79 (d, 1H), 7.73 (br s, 2H), 8.30 (s, 1H); ^{13}C NMR (Me_2SO-d_6) δ 61.4, 70.5, 73.6, 85.8, 87.2, 119.0, 120.9, 139.4, 149.7, 155.9; UV (EtOH) λ_{max} 264 nm (ε 13, 100).

2-Ethynyladenosine: A 250 mL RB flask was charged with 2.433 g (6.12 mmol) of 2-iodoadenosine in an inert atmosphere (N_2) in a glove box and 0.360 g (0.31 mmol) of tetrakis(triphenylphosphine) palladium catalyst and 0.094 g (0.50 mmol) of copper iodide was added to the flask. Dimethylformamide (20 mL) was then added, followed by triethylamine (1.0 mL, 6.81 mmol) and trimethylsilylacetylene (3.5 mL, 24.75 mmol) by syringe. The reaction flask was placed in an 80 °C oil bath and allowed to stir for 70 min. At this time, the solvent was removed and the residue was taken up in ethyl acetate and washed with 10% aqueous sodium EDTA solution. The ethyl acetate layer was dried over sodium sulfate and the solvent was removed to gave a brown solid. This residue was taken up in 10 mL of CH_3CN and treated with 1.020 g (6.81 mmol) of Et_4NF. The reaction mixture was allowed to stir at ambient temperature for 3 h. Reduction of solvent followed by separation and purification by column chromatography on silica gel (0-10 % MeOH/$CHCl_3$) gave 2-ethynyladenosine[16] as a light yellow solid 1.152 g (64 %): mp > 200 (decomp) ; ^1H NMR (Me_2SO-d_6) 3.63 (m, 2H), 3.95 (q, 1H), 4.13 (q, 1H), 4.54 (q, 1H), 5.15 (m, 2H), 5.42 (d, 1H), 5.85 (d, 1H), 7.50 (br s,2H), 8.45 (s, 1H); UV (EtOH) λ_{max} 262 nm, 286 nm (shoulder).

General Proceedure for the Synthesis of 2-Substituted Analogs of Adenosine: A 100 mL RBF was charged with 2-ethynyladenosine (1 mmol) and placed under N_2 in a glove box. Under inert atmosphere conditions, 0.05 mmol of $Pd(PPh_3)_4$, 0.08 mmol of CuI, and 0.1 mmol of LiCl was added to the flask. The solids were taken up in DMF (10 mL) and then 1.1 mmol of triethylamine was added by syringe. The desired triflic enolate (4 mmol) was then added to the mixture and the RBF was lowered into an 80 °C oil bath. Reaction progress was followed by TLC (10 % MeOH/$CHCl_3$). Upon completion, the solvent was removed under reduced pressure and the residue was taken up in EtOAc. The organic layer was washed (3 x 30 mL) with 10 % sodium EDTA solution, dried over $MgSO_4$, and the solvent was evaporated. Purification on a silica gel column (0-15% MeOH/$CHCl_3$) gave a light yellow solid (see Table 1).

2-(2-Cyclopentenylethynyl)adenosine: m.p. 157-159 °C; ^1H NMR (Me_2SO-d_6); 1.96 (m, 2H), 3.66 (dm, 2H), 3.97 (q, 1H), 4.15 (q, 1H), 4.51 (q, 1H), 5.08 (t, 1H), 5.21 (d, 1H), 5.52 (d, 1H), 5.98 (d, 1H), 6.44 (s, 1H), 8.69 (s, 1H); UV(EtOH) 296 nm (ε 20,900), 311nm (sh) (ε 15,500). Anal. Calcd for $C_{17}H_{19}N_5O_4$: C, 57.14; H, 5.36; N, 19.60. Found: C, 56.94; H, 5.27; N, 19.29.

2-(2-(1-Cyclohexenylethynyl)adenosine. m.p. 119-120 °C; ^1H NMR (Me_2SO-d_6) δ 1.61 (m, 4H), 2.30 (m, 4H), 3.66 (m, 2H), 3.96 (q, 1H), 4.15 (q, 1H), 4.52 (q, 1H), 5.08 (t, 1H), 5.22 (d, 1H), 5.51 (d, 1H), 5.95 (d, 1H), 6.40 (br s, 1H), 8.67 (s, 1H); UV (EtOH), 297 nm (ε 17,300), 311nm (sh) (ε 13,100). Anal. Calcd for $C_{18}H_{21}N_5O_4$: C, 58.21; H, 5.70; N, 18.86. Found: C, 57.87; H, 6.00; N, 18.45.

2-[2-(3,4-Dihydronaphthalenyl)ethynyl]adenosine: m.p. 120-123 °C; ^1H NMR (Me_2SO-d_6) δ 2.4 (m, 2H), 2.8 (m, 2H), 3.7 (m, 2H), 4.0 (q, 1H), 4.2 (m, 1H), 4.6 (q, 1H), 5.1 (t, 1H), 5.25 (d,1H), 5.6 (d, 1H), 6.0 (d, 1H), 6.8 (t, 1H), 7.3 (m, 4H); UV (EtOH) 274 nm (ε 12,700), 306 nm (ε 8,700), 321 nm (ε 7,600). Anal. Calcd for $C_{22}H_{21}N_5O_4 \cdot H_2O$: C, 60.40; H, 5.30; N, 16.01. Found: C, 60.10; H, 4.98; N, 15.73.

2-(2-Cyclododecenylethynyl)adenosine: m.p. 156-158 °C; ^1H NMR (Me_2SO-d_6), 1.3 (m, 22H), 2.3 (m, 2H), 3.6 (m,2H), 3.9 (s, 1H), 4.15 (m, 1H), 4.5 (m, 1H), 5.1 (t, 1H), 5.25 (d, 1H), 5.6 (d, 1H), 5.95 (d, 1H), 6.1 (d, 1H), 8.3 (s, 1H); UV (EtOH) 299 nm (ε 16,000), 312 nm (sh) (ε 12,700). Anal. Calcd for $C_{24}H_{33}N_5O_4 \cdot 0.5\ H_2O$: C, 62.05; H, 7.38; N, 15.08. Found: C, 62.89; H, 7.42; N, 14.98.

2-(2-Cycloheptenylethynyl)adenosine: m.p. 132-134 °C; ^1H NMR (Me_2SO-d_6) δ 1.54 (m, 4H), 1.74 (m, 2H), 2.25 (m, 2H), 2.39 (m, 2H), 3.64 (m, 2H), 3.95 (q, 1H), 4.12 (q, 1H), 4.53 (t, 1H), 5.22 (m, 2H), 5.45 (t, 1H), 5.86 (d, 1H), 6.47 (t, 1H), 7.47 (br s, 2H), 8.40 (s, 1H); UV (EtOH) 291 nm (ε 15,300), 301 nm (sh)

(14,950). Anal. Calcd for $C_{19}H_{23}N_5O_4 \cdot 0.5\ H_2O$: C, 57.86; H, 6.13; N, 17.76. Found: C, 58.75; H, 6.36; N, 17.77.

Example of Preparation of Triflic Enolate: Cyclohexanone (32.13 mmol) was combined with pyridine (35.34 mmol) in 50 mL of CH_2Cl_2 and chilled to -78° C. After 0.5 h in the cold bath, 5 mL (35.34 mmol) of triflic anhydride in 20 mL of CH_2Cl_2 was added over 1 hr. The solution was then allowed to warm to 25°C and stirred for 22 h. The reaction mixture was evaporated *in vacuo* and the residue was taken up in pentane. After filtration, the solid material was washed with pentane (2 x 20 mL). The combined organic layers were dried over $MgSO_4$ and the the solvent was removed to give 1-cyclohexenyl-1-yl triflate as a clear oil (41% yield): ^1H NMR($CDCl_3$) δ 1.59 (m, 2H), 1.75 (m, 2H), 2.16 (m,2H), 2.30 (m, 2H), 5.73 (m, 1H).

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References

1. Williams, M. Adenosine receptors: an historical perspective. *In Adenosine and Adenosine Receptors*; William, M., Ed.; Humana Publishing: Clifton, New Jersey, 1990: pp 1-17.
2. Jacobson, K.A.; van Galen, P.J.M.; Williams, M. *J. Med. Chem.* **1992**, *35*, 407.
3. Gustaffson, L. E.; Wiklund, C. U.; Wiklund, N. P.; Stelius, L. Subclassification of neuronal adenosine receptors. *In Purines in Cellular Signalling. Targets for New Drugs;* Jacobsen, K. A.; Daly, J. W.; Manganiello, V., Eds.; Springer Verlag: New York, 1990: pp 200-205.
4. Ribeiro, J. A.; Sebastiao, A. M. *Prog. Neurobiol.* **1986**, *26*, 179.
5. Trivedi, B. K.; Bridges, A. J.; Bruns, R. F. Structure activity relationships of adenosine A_1 and A_2 receptors. *In Adenosine and Adenosine Receptors*; William, M., Ed.; Humana Publishing: Clifton, New Jersey, 1990: pp 57-103.
6. Van Galen, P. J. M.; Leusen, F. J. J.; Ijzerman, A. P.; Soudijn, W. Eur. *J. Pharmacol.* **1989**, *172*, 19-27.
7. Ueeda, M.; Thompson, R. D.; Arroyo, L. H.; Olsson, R. A. *J. Med. Chem.* **1991**, *34*, 1340, 1340.
8. Abiru, T.; Yamaguchi, T.; Watanabe, Y.; Koji, K.; Aihara, K.; Matsuda, A. *Eur. J. Pharmacol.* **1991**, *196*, 69.
9. Francis, J. E.; Webb, R. L.; Ghai, G. R.; Hutchinson, A. J.; Moskal, M. A.; de Jesus, R.; Yokoyama, R.; Rovinski, S. L.; Contando, N.; Dotson, R.; Barclay, B.; Stone, G. A.; Jarvis, M. F. *J. Med. Chem.* **1991**, *34*, 2570.
10. Nair, V; Turner, G.A.; Chamberlain, S.D. *J. Am. Chem. Soc.* **1987**, *109*, 7223.

11. Nair, V.; Turner, G. A.; Buenger, G. S.; Chamberlain, S. D. *J. Org. Chem.* **1988**, *53*, 3051.

12. Homma, H.; Watanabe, Y.; Abiru, T.; Murayama, T.; Nomura, Y.; Matsuda, A. *J. Med. Chem.* **1992**, *35*, 2881.

13. Cristalli, G.; Eleuteri, A.; Vittori, S.; Volpini, R.; Lohse, M.J.; Klotz, K-N. *J. Med. Chem.* **1992**, *35*, 2363.

14. Abiru, T.; Miyashita, T.; Watanabe, Y.; Yamaguchi, T.; Machida, H.; Matsuda, A. *J. Med. Chem.* **1992**, *35*, 2253.

15. Matsuda, A.; Shinozaki, M.; Yamaguchi, T.; Homma, H.; Nomoto, R.; Miyasaka, T.; Watanabe, Y.; Abiru, T. *J. Med. Chem.* **1992**, *35*, 241.

16. Matsuda, A.; Shinozaki, M.; Miyasaka, T.; Machida, H.; Abiru, T. *Chem. Pharm. Bull.* **1985**, 33, 1766.

17. Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1988**, *110*, 1557.

18. Oh-e, T.; Miyaura, N.; Suzuki, A. *J. Org. Chem.* **1993**, *58*, 2201.

19. A very brief account of this work appeared in *Tetrahedron Lett.* **1995**, *36*, 6371-6372.

20. Stille, J. K. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508.

21. Robins, M. J.; Uznanski, B. *Can. J. Chem.* **1981**, *59*, 2601.

22. Nair, V.; Young, D. A. *J. Org. Chem.* **1984**, *50*, 406.

23. Nair, V.; Purdy, D. F. *Tetrahedron* **1991**, *47*, 365.

24. Stang, P. J.; Deuber, T. E. *Organic Synthesis* **1974**, *54*, 79.

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