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Regiospecific Michael Additions with 2-Aminopurines

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Abstract: N-9 alkylated materials are the sole products obtained from extended reaction of 2-aminopurines (potential guanine precursors) with Michael acceptors. This was used as the basis for a highly regioselective synthesis of famciclovir, the oral form of the anti-herpesvirus agent penciclovir.

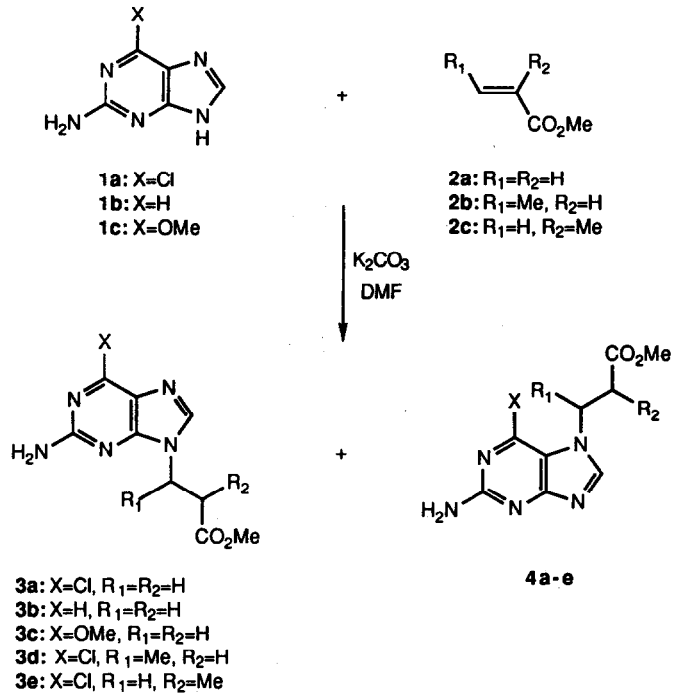
N-9 Alkylation of purines serving as guanine precursors is the primary route to pharmaceutically important acyclic nucleoside analogues, e.g. the guanine based anti-viral compounds acyclovir, ganciclovir and penciclovir,[1] but these reactions are rarely regiospecific. In particular the alkylation of 2-aminopurines usually gives rise to mixtures of N-9 and N-7 materials, (albeit with the desired N-9 isomers as the major products),[2] the separation of which requires tedious chromatography or fractional crystallisation.

Exclusive formation of N-9 alkylated products has been reported for the Michael reaction between 6-chloropurine and acrylonitrile,[3] and between adenine and four separate Michael acceptors.[4] More recently however, mixtures of N-9 and N-7 alkylated products have been obtained from Michael reactions with N-2 acylated guanines.[5] We have investigated the reaction between certain 2-aminopurines and simple Michael acceptors to determine whether N-9 specific alkylation is possible with this important class of purines, and to indicate the possibility of the wider synthetic utility of this reaction.

As a paradigm 2-amino-6-chloropurine **1a** was reacted with methyl acrylate **2a** (1.3 equivalents) in the presence of potassium carbonate (1 equivalent) in N,N-dimethylformamide at ambient temperature, Scheme 1. Examination of the reaction mixture by reverse-phase h.p.l.c. at regular intervals indicated that consumption of the purine ceased after 2.5 hours (20% **1a** remaining thereafter). The N-9:N-7 product ratio **3a**:**4a**, however, changed from 4.3:1 at 1 hour, through 24:1 at 24 hours to >200:1 at 48 hours (no **4a** detected).[6] By increasing the quantity of methyl acrylate **2a** used to eleven equivalents, no further consumption of **1a** was evident after 1 hour (8% remaining) and the presence of **4a** eliminated in 24 hours, giving **3a** in an isolated yield of 85%.

Temperature changes had a marked effect, at 50° (using 1.3 equivalents of **2a**) consumption of **1a** ceased in 20 minutes and **4a** was not detected after 3 hours, but 56% **1a** remained unreacted. At 0° **1a** reached a minimum level of 20% after 5 days, and the N-9:N-7 ratio proceeded from 2.6:1 at 1 hour to 19:1 at 6 days, at which time the reaction was terminated.

These findings are readily explained by the reversible nature of the Michael reaction, which allows the thermodynamically favoured N-9 product **3a** to be formed exclusively on achieving equilibrium. Entropy considerations favour the two-component system **1a** + **2a** at elevated temperatures.



Scheme 1

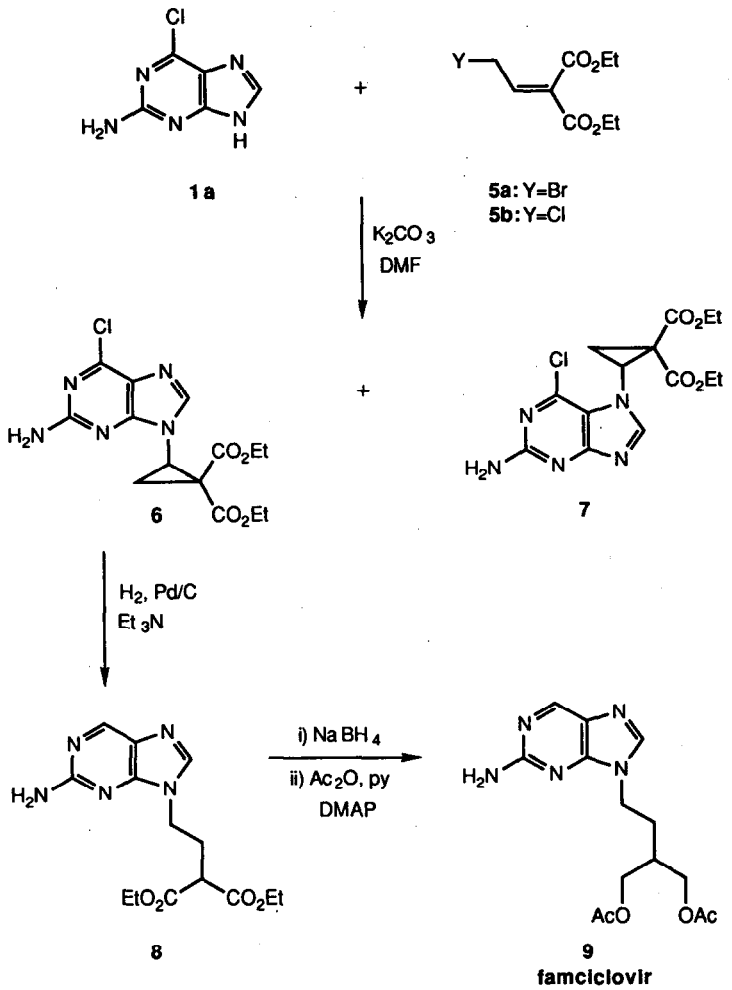
Replacement of **1a** with 2-aminopurine **1b** or 2-amino-6-methoxypurine **1c**, which are less N-9 regioselective in conventional N-alkylations[2] gave on reaction with **2a** a similar pattern of increasing N-9:N-7 product ratio with time. In these instances, however, the initial preference was for N-7 alkylation (**3b**:**4b** and **3c**:**4c** 1:1.1 after one hour), and the progression towards a single product much slower (incomplete after 14 days at ambient temperature).[7]

Reactions between **1a** and the more sterically-demanding methyl crotonate **2b** and methyl methacrylate **2c** were much slower than with **2a**, and showed good N-9 regioselectivity from the outset, but again an N-9:N-7 product ratio which increased with time was observed.

These findings were applied to furnish a highly regioselective synthesis of famciclovir, the oral form of the anti-herpesvirus agent penciclovir.[8]

2-Bromoethylidene malonate esters have been shown to react with a variety of nucleophiles to provide the corresponding 2-substituted cyclopropane-1,1-dicarboxylic esters by a mechanism of Michael addition followed by ring closure.[9] When **1a** was reacted with **5a** (1.1 equivalents) an 8:1 mixture of the N-9 and N-7 cyclopropyl purines **6** and **7** was produced in an overall yield of 87%, Scheme 2.[10] This ratio is superior to the 4 or 5:1 usually found with conventional N-alkylations of **1a**, but it was felt that further improvement could be obtained by substituting a poorer leaving group for bromine in **5a**, thereby allowing the Michael reaction to proceed more towards equilibrium prior to the irreversible ring closure. Accordingly, the chloroethylidene malonate **5b** was prepared by the method described for similar compounds,[11] and then reacted with **1a** as previously, providing **6** and **7** on this occasion in a ratio of 40:1.

Catalytic hydrogenation of **6** in the presence of base effected both dehalogenation and 1,2-cyclopropane bond fission to provide **8** in a yield of 74%.[12] Diester reduction and O-acetylation were achieved without isolation of the intermediate diol to give 82% of famciclovir **9** as colourless crystals, m.p.102-103°.[8]



Scheme 2

The concept of regiospecific Michael addition with purines should be extendable to other heterocycles where the thermodynamically favoured isomer is required. The finding that product mixtures were obtained with N-2 acylated guanines[5] may indicate that in this case the isomers have similar energies of formation.

Acknowledgements

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References and Notes

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6. By stopping a reaction after 2 hours, followed by filtration, evaporation and separation by column chromatography, pure samples of **3a** and **4a** were obtained. U.V. spectra of **1a**, **3a** and **4a** were determined and the h.p.l.c. data corrected for molar extinction coefficient differences at the detection wavelength (254 nm). Selected analytical data for **3a** and **4a**:[13] **3a**; δ_H(DMSO-d_6) 2.95(t,2H,CH_2CO), 3.60(s,3H,CH_3), 4.30(t,2H,CH_2N), 6.98(brs,2H,NH_2), 8.12(s,1H,H-8).; δ_C 32.93($\underline{C}H_2CO$), 39.01(CH_2N), 51.68(CH_3), 123.28(C-5), 143.31(C-8), 149.32(C-6), 154.02(C-4), 159.77(C-2), 171.01(CO). **4a**; δ_H 2.95(t,2H,CH_2CO), 3.60(s,3H,CH_3), 4.55(t,2H,CH_2N), 6.63(brs,2H,NH_2), 8.33(s,1H,H-8).; δ_C 34.81($\underline{C}H_2CO$), 41.85(CH_2N), 51.66(CH_3), 114.69(C-5), 142.09(C-6), 149.74(C-8), 159.97(C-2), 164.23(C-4), 170.83(CO).
7. Consumption of the starting purines **1b** and **1c** proceeded to completion, no **1b** or **1c** being detected after 24 hours.
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10. **6**; δ_H(DMSO-d_6) 0.77(t,3H,CH_3), 1.23(t,3H,CH_3), 2.03(dd,J = 6.9,8.5Hz,1H,cyclopropyl CH_2), 2.81(t,J = 6.5Hz,1H,cyclopropyl CH_2), 3.82(q,2H,ester CH_2), 4.20(dq,2H,ester CH_2), 4.37(dd,J = 6.2, 8.5Hz,cyclopropyl CH), 7.02(brs,2H,NH_2), 8.15(s,1H,H-8).; δ_C 13.22(CH_3), 13.85(CH_3), 17.64(cyclopropyl CH_2), 35.12(cyclopropyl C), 37.06(cyclopropyl CH), 61.30(ester CH_2), 61.73(ester CH_2), 123.26(C-5), 142.52(C-8), 149.39(C-6), 155.05(C-4), 159.92(C-2), 164.76(CO), 167.35(CO). **7**; δ_H(DMSO-d_6) 0.68(t,3H,CH_3), 1.22(t,3H,CH_3), 2.11(dd,J = 7.0,8.4Hz,1H,cyclopropyl CH_2), 2.83(t,J = 6.6Hz,1H,cyclopropyl CH_2), 3.78(dq,2H,ester CH_2), 4.22(dq,2H,ester CH_2), 4.65(dd,J = 6.2, 8.3Hz, cyclopropyl CH), 6.43(brs,2H,NH_2), 8.50(s,1H,H-8).; δ_C 13.08(CH_3), 13.94($\underline{C}H_3$), 18.08(cyclopropyl CH_2), 35.86(cyclopropyl C), 40.10(cyclopropyl CH), 61.24(ester CH_2), 61.58(ester CH_2), 115.81(C-5), 143.11(C-6), 148.15(C-8), 160.16(C-2), 164.09(C-4), 164.50(CO), 166.95(CO).
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12. **8**; δ_H(DMSO-d_6) 1.13(t,6H,2xCH_3), 2.33(q,2H,$C\underline{H}_2CH$), 3.47(t,1H,CH), 4.04(dq,4H,2x ester CH_2), 4.13(t,2H,CH_2N), 6.47(brs,2H,NH_2), 8.00(s,1H,H-8), 8.56(s,1H,H-6).; δ_C 13.66(2xCH_3), 27.84($\underline{C}H_2CH$), 40.28(CH_2N), 48.76(CH), 61.07(2x ester CH_2), 126.75(C-5), 142.49(C-8), 148.86(C-6), 152.92(C-4), 160.36(C-2), 168.22(2xCO).
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