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A new asymmetric 1,4-addition method: application to the synthesis of the HIV non-nucleoside reverse transcriptase inhibitor DPC 961

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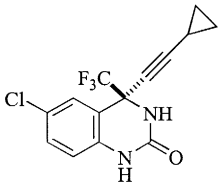
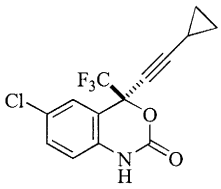
Abstract

The asymmetric synthesis of the HIV non-nucleoside reverse transcriptase inhibitor (NNRTI) DPC 961 is achieved in three steps with an overall yield of >55%. The asymmetry is induced by the chiral auxiliary (*R*)-(+)-α-methylbenzylamine, utilizing a new asymmetric 1,4-addition protocol.

The dihydroquinazolinone DPC 961[1a] **1** is a second generation HIV non-nucleoside reverse transcriptase inhibitor (NNRTI) with enhanced potency when compared to Efavirenz (Sustiva™) which has been approved for the treatment of HIV.[2] DPC 961[1a] is currently undergoing clinical evaluation due to its activity against wild-type HIV-1 and increased potency toward the K103N-containing human immunodeficiency virus as well as a variety of NNRTI-resistant mutant viruses. This communication describes a highly stereoselective synthesis of DPC 961.[1a,b]



DPC 961



Efavirenz (Sustiva™)

1

Although the general synthetic transformations outlined in Scheme 1 have literature precedent,[3,4] no examples are known in which R^2 is chiral or 1,4-additions to **3** yield **4** diastereoselectively. We decided to investigate the synthesis of DPC 961[1a] using the approach outlined in Scheme 1 with R^2 as an acid labile chiral auxiliary to direct a diastereoselective 1,4-addition of R^3M to the 2(3*H*)-quinazolinone **3**.

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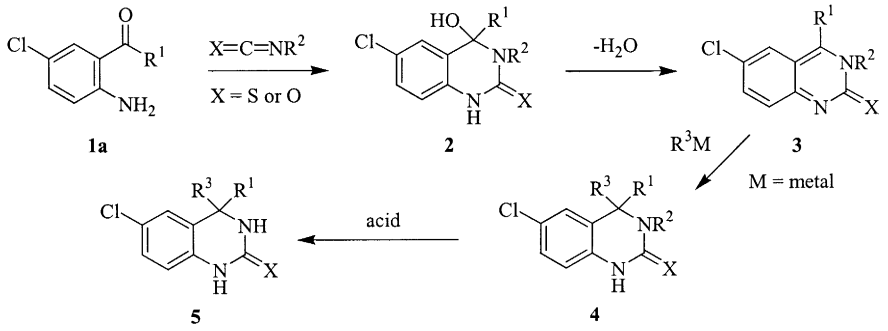
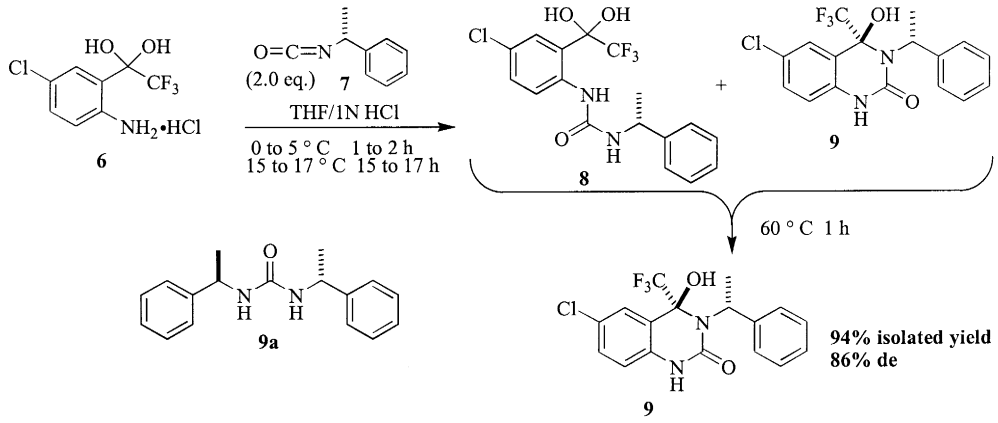


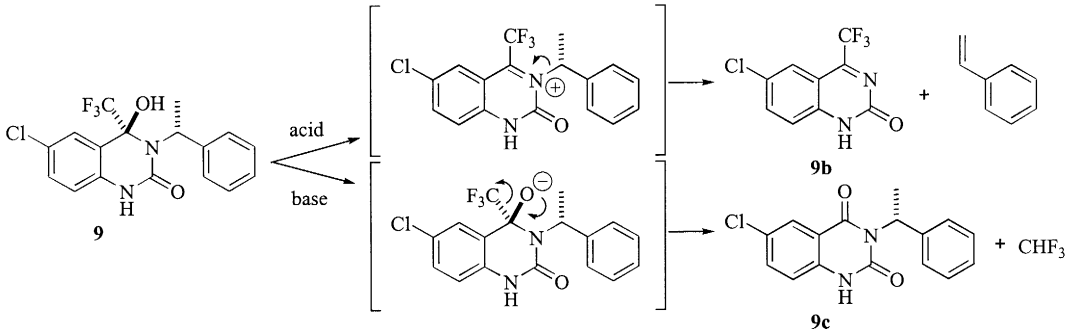
Scheme 1.

The keto-aniline **1a**[2] (Scheme 1) where $R^1=CF_3$ is unreactive towards (*R*)-(+)-α-methylbenzyl isocyanate **7** (Scheme 2), presumably due to delocalization of the nitrogen lone pair of **1a** into the trifluoromethyl ketone. The hydrate hydrochloride keto-aniline **6** (Scheme 2) is a known compound[2b] and reacts with isocyanate **7** in aqueous acidic solvents, preferably THF containing 7% vol. 1N HCl. A >95% conversion of hydrate hydrochloride **6** into acyclic urea **8** (which cyclizes to give hemiaminal **9**) requires two equivalents of isocyanate **7**, because one of the equivalents is hydrolyzed to give (*R*)-(+)-α-methylbenzylamine hydrochloride and CO_2 under the reaction conditions. Temperatures in excess of 25°C prior to consumption of the isocyanate **7** led to its decomposition to give the corresponding symmetric urea **9a** which is difficult to separate from the product. After consumption of the isocyanate **7**, the acyclic urea **8** is converted rapidly (within 1 h) to the hemiaminal **9** by increasing the temperature to 60°C. The hemiaminal moiety of **9** is formed diastereoselectively in a ratio of 93:7. The absolute configuration of the major diastereomer of **9** was determined by X-ray. After washing the (*R*)-(+)-α-methylbenzylamine hydrochloride away with water, crystallization of hemiaminal **9** is effected by exchanging the THF for toluene via azeotropic distillation to give a 94% isolated yield of hemiaminal **9** as a 96:4 ratio of diastereomers.



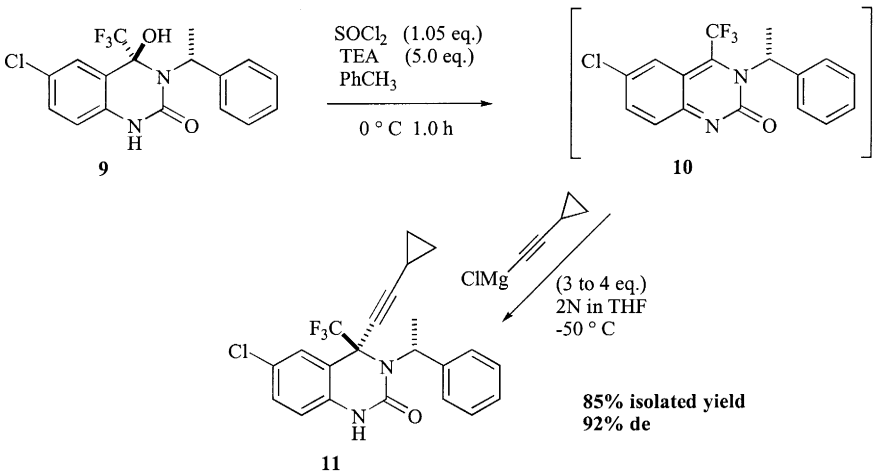
Scheme 2.

The literature describes 1,4-dehydration of cyclic hemiaminals related to **9** under acidic, basic, or thermal conditions.[3–5] Although the hemiaminal **9** did not dehydrate thermally, exposure to acid caused 1,2-dehydration to form the corresponding iminium ion, and the benzyl group was cleanly lost via ionization, generating styrene/polystyrene and the ketimine **9b** (Scheme 3). Treatment of **9** with base generated the alkoxide which eliminated fluoroform to give the corresponding imide **9c** (Scheme 3) at room temperature in excellent yield.



Scheme 3.

In order to prevent the fluoroform elimination pathway and promote the 1,4-dehydration, the alkoxide of **9** was generated at low temperature and trapped with an activating agent. The first example of this procedure was to dissolve **9** in THF, in the presence of excess TEA at 0°C, and treat the colorless mixture with methanesulfonyl chloride. This produced a bright orange mixture that became colorless upon exposure to air and returned the starting material **9**. Extended imines of type **10** (Scheme 4), known as substituted 2(3*H*)-quinazolinones, are reported to be highly colored compounds ranging from yellow to red.[3–5] 2(3*H*)-Quinazolinones have been isolated,[3,4] but this particular analog bearing a trifluoromethyl group has proven too reactive for practical isolation. Therefore, 2(3*H*)-quinazolinone **10** was treated in situ with cyclopropylacetylide which afforded the desired dihydroquinazolinone **11** with a high degree of diastereoselectivity.

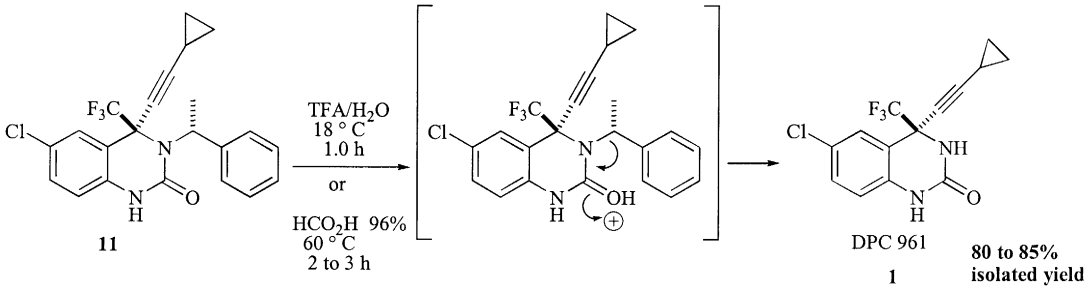


Scheme 4.

Scheme 4 depicts the optimized preparation of dihydroquinazolinone **11**.[6] The hemiaminal **9** is suspended in toluene, and treated with an excess of TEA as solvent and base. Exposure of this mixture at 0°C to an equivalent of thionyl chloride rapidly generates intermediate **10** which is trapped instantaneously at −50°C by an excess of cyclopropylacetylene magnesium chloride to give **11**. Employing the optimized procedure, the conversion of **9** into **11** is 97%, and the diastereomeric excess is routinely around 92%. The dihydroquinazolinone **11** is crystallized from methanol to give an 86% isolated yield of the desired diastereomer exclusively (absolute configuration confirmed by X-ray). The reaction has been run with a ReactIR 1000 DiComp® probe submerged into a mixture of **9** in toluene containing triethylamine at 0°C. The absorptions corresponding to the carbonyl and NH stretching vibrations were recorded at 1681 cm^{-1}

and 3200 cm^{-1}, respectively. Addition of thionyl chloride to the mixture caused the carbonyl absorption at 1681 cm^{-1} to disappear (as well as the NH absorption) and a new carbonyl absorption to appear at 1696 cm^{-1}. The increased carbonyl absorption of 15 cm^{-1}, indicating a lessening mesomerism or more carbonyl characteristic, and the disappearance of the NH absorption supports intermediate **10**.

As illustrated in Scheme 5, the conversion of dihydroquinazolinone **11** into DPC 961[1a] is effected by acid. Trifluoroacetic acid (TFA) is the usual acid used for such transformations.[4] Exposure of **11** to wet TFA at 18°C causes complete deprotection within 1 h. We have obtained an 80% isolated yield of DPC 961[1a] using this procedure. Warm formic acid also induces ionization of the benzyl group to transform **11** into DPC 961,[1a] in 85% isolated yield.



Scheme 5.

This paper describes the first 1,4-asymmetric additions to substituted 2(3*H*)-quinazolinones to afford chiral dihydroquinazolinones. The HIV NNRTI DPC 961[1a] is prepared in three steps in >55% isolated yield using this methodology. This chemistry is amenable to large scale and has provided metric ton quantities of DPC 961.[1a] Further applications of this chemistry are under investigation and will be reported in due course.

Acknowledgements

Charles W. Ray and Robert G. Wethman are thanked for conducting and interpreting the IR experiment.

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6. Preparation of dihydroquinazolinone **11**: under N_2, the hemiaminal **9** (1.0 g, 2.70 mmol) is suspended in toluene (10 mL) and treated with triethylamine (TEA) (1.88 mL, 13.49 mmol) to give a colorless homogeneous mixture. The resulting mixture is cooled to 0°C, and thionyl chloride (206 μL, 2.83 mmol) added slowly. This produces a bright orange mixture with TEA hydrochloride salt as a precipitate. After 1 h at 0°C, the mixture is cooled to −50°C. A 2N cyclopropylacetylene magnesium chloride solution in THF (6.47 mL, 10.79 mmol) is added to the mixture over 0.5 h. The resulting mixture is quenched into 12% aqueous citric acid (10 mL). The organic phase is concentrated via distillation and the remaining solvent subsequently exchanged for methanol employing azeotropic distillation. This induces crystallization of the product **11** in 86% (970 mg) isolated yield. The de of **11** in the crude reaction mixture was determined to be 92% by HPLC using a Zorbax RX-C18 column.