o-NITROPHENYLTRIFLATES IN QUINOLINE SYNTHESIS : EASY ACCESS TO A STREPTONIGRIN SYNTHON

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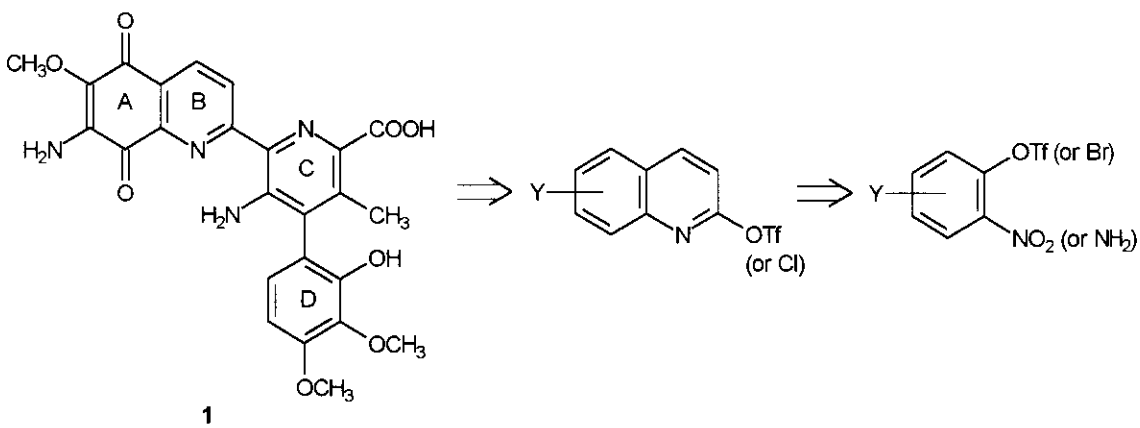
Abstract- An efficient route to a wide range of 2-hydroxyquinolines from *o*-nitrophenyltriflates *via* a Heck reaction is reported, with emphasis on the preparation of a synthetic equivalent of the streptonigrin AB ring system.

Streptonigrin (**1**) is a highly functionalised tetracyclic compound which shows potent anticancer activity.[1] Whereas previous total syntheses[2] involved complex ring forming reactions and functional group manipulations, our overall strategy is more convergent and based on the use of preformed rings. As part of our investigation, preparation of the AB quinoline-quinone structure came under attention. Our strategy involves the Heck reaction[3] of an appropriately-substituted benzene with methyl acrylate, followed by cyclisation, to afford a substituted 2-hydroxyquinoline which can be converted into the reactive 5,8-dione in the latter stages of the synthesis. Conversion of the 2-hydroxyquinoline into the 2-chloro or 2-triflyl derivative would provide a suitable substrate for palladium catalysed cross coupling to the CD moiety.



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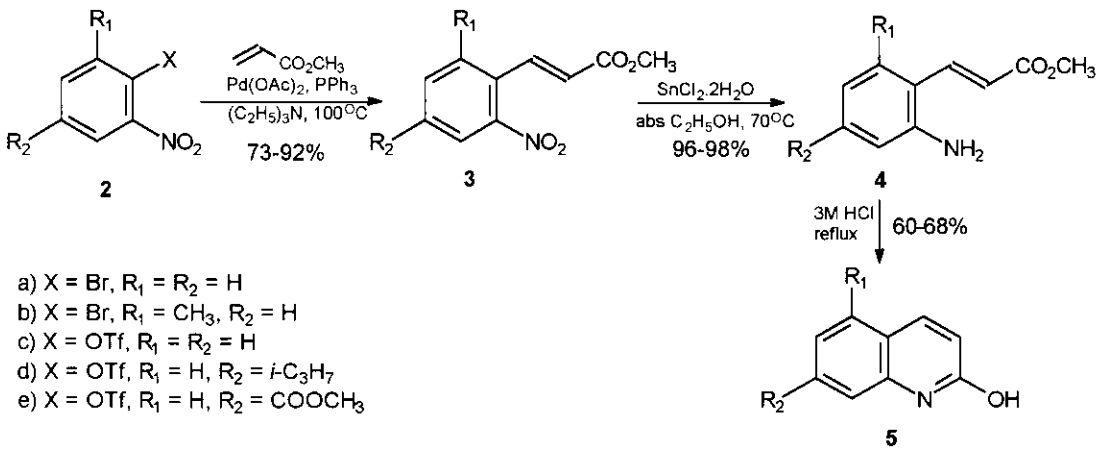
It is well known that electron-rich substrates react poorly under standard Heck conditions.[4] Initial model work on the Heck reactions of various aryl bromides and triflates confirmed that *o*-nitro compounds

afforded higher yields under milder conditions than the corresponding *o*-amines and protected amines. Reactions of the *o*-nitrophenyltriflates were also found to be comparable to those of the corresponding bromides. These results prompted the selection of five model substrates to test the proposed route: two *o*-bromonitrobenzenes (**2a-b**) and three *o*-nitrophenyltriflates (**2c-e**), where the latter were prepared from the corresponding phenols in good yields *via ortho*-nitration and triflation.[5] In all cases the Heck reaction proceeded smoothly, with only compound (**2b**) giving relatively lower yields due to steric hindrance. Reduction to aminocinnamates (**4a-e**) was near quantitative using tin(II) chloride dihydrate,[6] and the cyclisation step proceeded in reasonable yields with some recovery of starting material. Esterification (diazomethane) of the crude product was required for isolation of **5e**.[7]

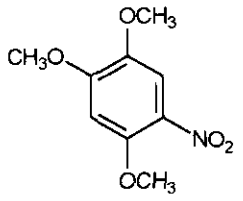


a) X = Br, $R_1 = R_2 = H$
b) X = Br, $R_1 = CH_3$, $R_2 = H$
c) X = OTf, $R_1 = R_2 = H$
d) X = OTf, $R_1 = H$, $R_2 = i\text{-}C_3H_7$
e) X = OTf, $R_1 = H$, $R_2 = COOCH_3$

The success achieved with these substrates suggests that the route may be applied to a wide range of compounds, and highlights in particular the versatility of *o*-nitrophenyltriflates as intermediates. A very limited selection of *o*-bromonitrobenzenes and *o*-bromoanilines is commercially available, and bromo compounds have been increasingly targeted as being environmentally unfavourable. Alternatively, the use of DOM methodology[8] to introduce a halogen *ortho* to an amine is expensive and tedious. However, a wide range of commercially available and inexpensive phenols readily undergo *ortho* nitration. Subsequent triflation of these nitrophenols provides rapid access to suitable Heck substrates.

Extension of the Heck route to the streptonigrin problem required the selection of possible substrates. Previously, Godard *et al.* reported the synthesis of a potential streptonigrin AB ring precursor *via* a similar approach, starting from 1,2,4-trimethoxy-3,5-dinitrobenzene.[9] In this case, reduction of the nitro groups and introduction of an iodide by DOM methodology afforded a Heck substrate which was converted into the desired quinoline. However, the starting material is not readily available and was prepared in 6 steps from guaiacol.[10] The direct dinitration of commercially available 1,2,4-trimethoxybenzene has not been reported in the literature, and while 2,4,5-trimethoxynitrobenzene (**6**) could be prepared in excellent yields

in our laboratory,[11] further nitration of the electron-rich substrate using a large variety of methods led only to the formation of an array of highly coloured oxidation products. The success of the *o*-nitrophenyltriflates prompted us to consider 3,5-dimethoxyphenol as a possible starting material. After extensive investigation of nitration conditions, compounds (**7a**) and (**7b**) were isolated in reasonable yields (62-80%) using nitronium tetrafluoroborate in dry DME.[12]



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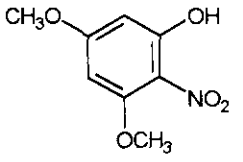
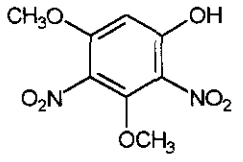
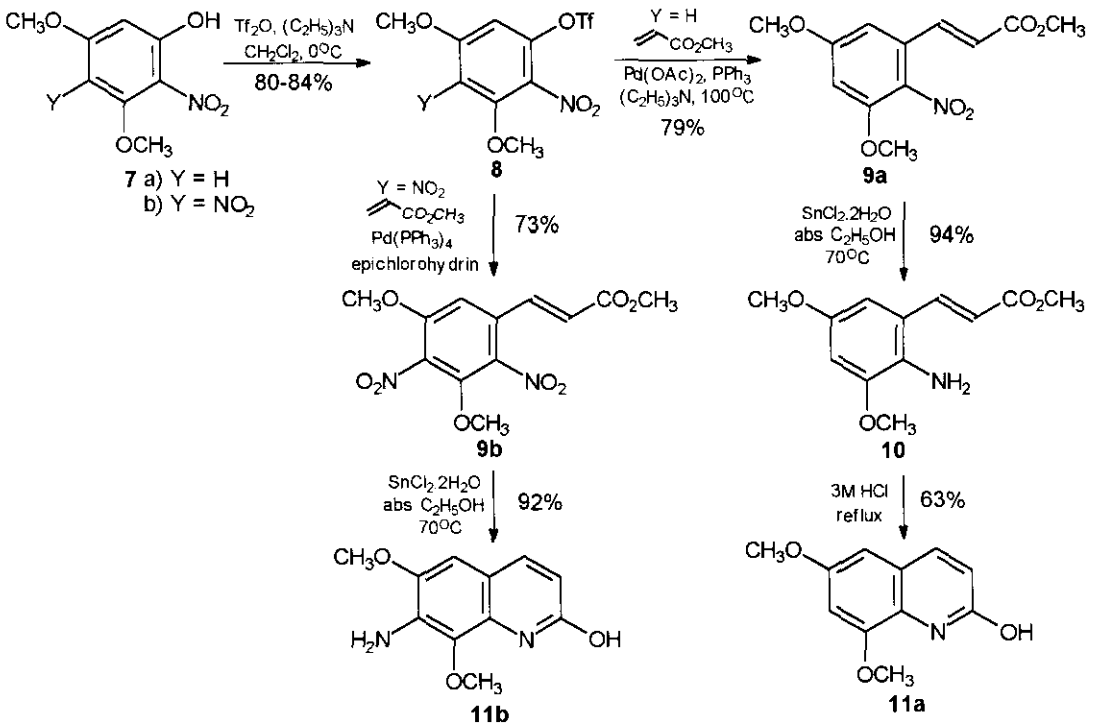


7a



7b

The triflation and subsequent Heck reaction of **7a** proceeded smoothly under the conditions employed for the model compounds. Reduction and acid-catalysed cyclisation of the Heck product afforded 2-hydroxyquinoline (**11a**)[13] in a good overall yield. The dinitro compound, however, posed some difficulties.



Triflation at 0°C was successful, but the Heck reaction failed altogether under the basic Heck conditions, due to rapid decomposition of the triflate. This instability of dinitrotriflates under basic conditions has been reported.[14] In an attempt to alleviate the problem, the possibility of performing a Heck reaction under neutral conditions was investigated, using epichlorohydrin as a proton scavenger.[15] Using 5 mol % $Pd(OAc)_2/PPh_3$, yields of the desired Heck product (**9b**) were in the order of 20-25%. Fairly rapid

deposition of palladium metal was observed, suggesting the epichlorohydrin was not as effective as triethylamine in regenerating the catalyst. However, changing the catalyst to $Pd(PPh_3)_4$ and increasing the amount of palladium to 20 mol % eventually produced optimal yields of 78%. Surprisingly, reduction of **9b** afforded the desired cyclised product (**11b**)[18] in yields in excess of 90%, in one step.

The route to the streptonigrin AB ring system has, therefore, provided a convenient synthetic equivalent from which to continue the total synthesis. An analogue of the CD moiety is presently being synthesised and will contain functionality to allow cross-coupling to the amine-protected 2-triflyl or 2-chloro derivative of **11b**. In this regard, we have found that 2-quinolyltriflates undergo smooth palladium catalysed cross coupling with (2-pyridyl)trimethylstannanes. A final oxidation step to the 5,8-quinone, for which there is literature precedent,[19] will afford the desired 5,8-quinone. The success of the *o*-nitrophenyltriflates in Heck reactions has prompted investigations into their potential in cross coupling reactions, as the mechanisms involve the same initial palladium insertion step. It is believed that they hold great potential for the synthesis of a variety of hetero- and carbocyclic compounds due to the rich chemistry of the *o*-nitro group.

ACKNOWLEDGEMENTS

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5. Compound (**2c**) was obtained *via* standard triflation (Tf_2O/2,4,6-collidine/CH_2Cl_2/0°C) of commercially available 2-nitrophenol. Compound (**2d**) was prepared from 4-isopropylphenol *via* nitration ($Ca(NO_3)_2/H_2SO_4$ following the method of S.C.Bisarya, S.K.Joshi, and A.G.Holkar, *Synth. Commun.*, 1993, **23**, 1125), followed by triflation. Compound (**2e**) was prepared from 4-hydroxybenzoic acid methyl ester *via* nitration using a two phase system (HNO_3-AcOH in CH_2Cl_2, following the method of E.M.Hindmarsh, I.Knight, and R.Robinson, *J. Chem. Soc.*, 1917, **110**, 943), followed by triflation.

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7. For a representative example of NMR data see reference 12.
8. For a comprehensive review, see: V.Snieckus, *Chem. Rev.*, 1990, **90**, 879.
9. A.Godard, J.M.Fourquez, R.Tamion, F.Marsais, and G.Quéguiner, *Synlett*, 1994, 235.
10. T.Kametani and K.Ogasawara, *Yakugaku Zasshi*, 1965, **85**, 985 (*Chem. Abstr.*, 1966, **64**, 6611e).
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12. Compound (**7a**) was prepared by the addition of 1 mol equivalent $NO_2^+BF_4^-$ to a stirred solution of 3,5-dimethoxyphenol in dry DME. Compound (**7b**) was prepared by the addition of 2.5 mol equivalents $NO_2^+BF_4^-$ to a stirred solution of 3,5-dimethoxyphenol in dry DME.
13. **7a**: mp 59-62°C, ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.54 (1H, br s), 6.13 (1H, d, J=2.6 Hz), 6.00 (1H, d, J=2.7 Hz), 3.87 (3H, s), 3.82 (3H, s), ^{13}C NMR (300 MHz, $CDCl_3$): δ 165.90, 159.68, 158.06, 111.85, 93.67, 92.76, 56.65, 55.91, MS: m/z 199 (M^+); **8a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.52 (1H, d, J=2.4 Hz), 6.47 (1H, d, J=2.4 Hz), 3.90 (3H, s), 3.85 (3H, s), ^{13}C NMR (300 MHz, $CDCl_3$): δ 162.25, 154.26, 142.31, 120.48, 116.23, 99.40, 98.75, 56.90, 56.20, MS: m/z 331 (M^+); **9a**: mp 168-171°C, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55 (1H, d, J=15.9 Hz), 6.62 (1H, d, J=2.4 Hz), 6.54 (1H, d, J=2.4 Hz), 6.40 (1H, d, J=15.9 Hz), 3.87 (1H, s), 3.86 (1H, s), 3.76 (1H, s), ^{13}C NMR (300 MHz, $CDCl_3$): δ 166.07, 161.57, 153.00, 138.38, 137.46, 129.76, 123.22, 102.33, 100.90, 56.53, 55.83, 51.99, MS: m/z 267 (M^+); **10**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.85 (1H, d, J=15.9 Hz) 6.48 (1H, d, J=2.4 Hz), 6.44 (1H, d, J=2.4 Hz), 6.31 (1H, d, J=15.9 Hz), 3.81 (3H, s), 3.77 (3H, s), 3.74 (3H, s), ^{13}C NMR (300 MHz, $CDCl_3$): δ 167.92, 152.38, 148.96, 140.10, 128.60, 128.44, 117.51, 101.56, 100.89, 55.77, 55.59, 51.60, MS: m/z 237 (M^+); **11a**: mp >280°C, ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.15 (1H, br s), 7.65 (1H, d, J=9.6 Hz), 6.66 (d, 1H, J=9.3 Hz), 6.62 (1H, d, J=2.4 Hz), 6.53 (1H, d, J=2.4 Hz), 3.92 (3H, s), 3.82 (3H, s), ^{13}C NMR (300 MHz, $CDCl_3$): δ 161.70, 155.45, 146.55, 140.26, 123.65, 123.02, 119.96, 101.49, 99.60, 56.03, 55.66, MS: m/z 205 (M^+).
14. T.M.Chapman and E.A.Freedman, *Synthesis*, 1971, 591.
15. To our knowledge, there have been no reports in the literature of Heck reactions carried out under neutral conditions in the presence of a proton scavenger. Further investigations are being carried out to establish the generality of the method.
16. **11b**: mp >280°C, ^{1}H NMR (300MHz, $CDCl_3$): δ 9.85 (1H, s), 7.59 (1H, d, J=9.3 Hz), 6.64 (1H, s), 6.43 (1H, d, J=9.3 Hz), 4.35 (2H, s), 3.86 (3H, s), 3.82 (3H, s), ^{13}C NMR (300 MHz, $CDCl_3$): δ 163.11, 144.44, 140.75, 133.20, 131.23, 127.86, 117.08, 110.89, 102.89, 59.57, 55.86, MS: m/z 220 (M^+).
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