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Judicious Application of Allyl Protecting Groups for the Synthesis of 2-Morpholin-4-yl-4-oxo-4*H*-chromen-8-yl Triflate, a Key Precursor of DNA-Dependent Protein Kinase Inhibitors

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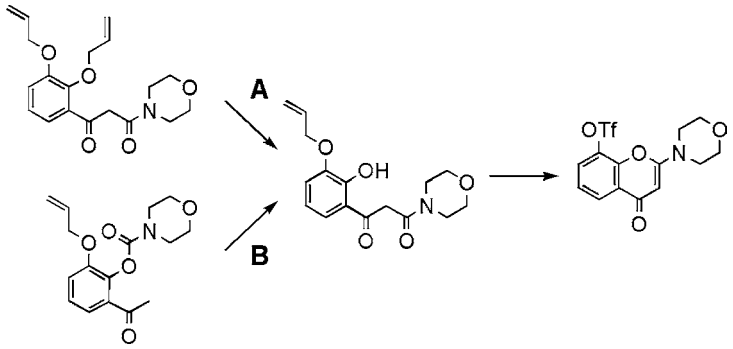
ABSTRACT



2-Morpholin-4-yl-4-oxo-4*H*-chromen-8-yl 2,2,2-trifluoromethanesulfonate is a key intermediate for the synthesis of the DNA-dependent protein kinase (DNA-PK) inhibitor 8-dibenzothiophen-4-yl-2-morpholin-4-yl-chromen-4-one (NU7441). Two improved methods for the synthesis of this triflate have been developed: (A) in 35% overall yield, through modification of the published route, and (B) in 15% overall yield, by a new route employing a Baker–Venkataraman rearrangement to enable generation of the chromenone scaffold. Both syntheses depend on the judicious use of allyl protecting groups.

DNA-dependent protein kinase (DNA-PK) is a nuclear serine/threonine kinase, which is activated by DNA double-strand breaks.[1] Inhibition of DNA-PK with ATP-competitive, small molecules potentiates DNA-damaging agents, such as ionizing radiation or alkylating agents, which are commonly used in cancer therapy.[2] We have reported potent, selective DNA-PK inhibitors based on a chromen-4-one scaffold, notably 8-dibenzothiophen-4-yl-2-morpholin-4-yl-chromen-4-one (**NU7441**, $IC_{50} = 12$ nM),[3,4] prepared via a Suzuki−Miyaura coupling between 2-morpholin-4-yl-4-oxo-4*H*-chromen-8-yl triflate (**1**) and 4-dibenzothiophene boronic acid (Scheme 1).

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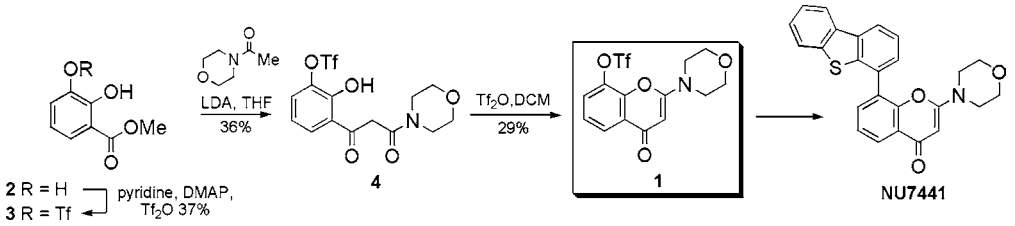
Scheme 1. Synthesis of 8-Dibenzothiophen-4-yl-2-morpholin-4-yl-chromen-4-one (**NU7441**)[3]



The synthesis of triflate **1** was achieved in three steps from methyl 2,3-dihydroxybenzoate (**2**) but in a poor overall yield (4%, Scheme 1).[3,4] There were problems with each step of this route: lack of selectivity in the conversion of ester **2** into **3**, a byproduct (di-*O*-triflate) being obtained in significant yield; the requirement for more than 2 equiv of the lithium enolate of *N*-acetylmorpholine, because of the deprotonation of the phenolic hydroxyl group of **3**; and the poor yield of **1** from the cyclization of ketoamide **4**.

As part of an ongoing program of optimization of DNA-PK inhibitors, we sought a more efficient route to **1**. On the basis of the premise that the cyclization of ketoamide **4** was impeded by the triflate group, replacement by the electron-releasing *O*-allyl group was regarded as potentially advantageous. Allyl was also chosen because of its stability under the strongly acidic and basic conditions required and its ability to be removed under specific conditions.[5] We envisaged that the intermediate allyl-protected ketoamide **7** (Scheme 2) could be accessed by two routes. One was a modification of the existing route to **4**,[3] and the other exploited the Baker−Venkataraman rearrangement.[6] Cyclization of **7**, followed by removal of the allyl protecting group and conversion of the liberated hydroxyl group into a triflate ester, would give the desired **1**.

Allyl protection of both hydroxyl groups in ester **2** was achieved in excellent yield under standard conditions[7] giving **5**. Reaction of **5** with the lithium enolate of *N*-acetylmorpholine gave ketoamide **6** in much improved yield (cf. Schemes 1 and 2). To remove the allyl group ortho to the carbonyl function of **6**, palladium catalysis[8] and DDQ[9] were initially tried. However, Pd removed both allyl groups from **6**, and DDQ gave unreacted starting material. The reagent $TiCl_4/Bu_4NI$ has been reported for the selective monodeprotection of diprenyl ethers.[10] We found that $TiCl_4/Bu_4NI$ accomplished selective deprotection of the *ortho*-allyl group of **6** to give phenol **7** in near quantitative yield. As suggested by Tsuritani et al.,[10] the selectivity results from the $TiCl_4$ coordinating to the keto group, preferentially activating the *ortho*-allyl group to nucleophilic displacement by iodide.

Selective protection of the 3-hydroxyl group of 2,3-dihydroxybenzaldehyde with allyl or benzyl has been reported.[11,12] However, the yield for allylation was 48%,[11] compared to the 86% or 89% overall yield obtained for the protection−deprotection sequence (Scheme 2). Although 73% was claimed for selective benzylation of 2,3-dihydroxybenzaldehyde at the 3-hydroxyl group,[12] in our hands only 27% was achieved.

An alternative route to **1** started with bisallyl protection of aldehyde **10**, giving **11** in excellent yield. Compound **11** was converted into the corresponding methyl ketone **12**, in 70% yield over two steps, by treatment with MeMgBr, followed by oxidation of the intermediate alcohol using pyridinium chlorochromate. Selective deprotection of one allyl group proceeded as described above, giving the acetophenone derivative **13**. Reaction of **13** with morpholine *N*-chloroformate gave the carbamate **14** in good yield. Baker−Venkataraman rearrangement of **14** was achieved by treatment with potassium hydroxide in pyridine, to give the ketoamide **7** in good yield.

Ring closure of **7** to the 8-allyloxy chromenone **8** was effected by treatment with triflic anhydride in DCM.[13] Removal of the *O*-allyl protecting group by a two-step procedure of isomerization to an *O*-propenyl intermediate effected by a suitable catalyst (e.g., Wilkinson's catalyst $[RhCl(PPh_3)_3]$;[14] ruthenium-based catalysts[15,16]), followed by mild acidic hydrolysis of the propenyl group to release hydroxyl, has often been reported. We have found that treatment of **8** with Wilkinson's catalyst and 1,4-diazabicyclo-[2.2.2]octane (DABCO) in EtOH gave 8-hydroxychromenone **9** directly in 93% yield, obviating the need for an acidic cleavage step. A limited study of the scope of this simplified method for removing allyl has shown that, for example, **15** can be deprotected to **16** in excellent yield (Scheme 3). Finally, compound **9** was converted into **1** using *N*-phenyltriflimide and triethylamine.

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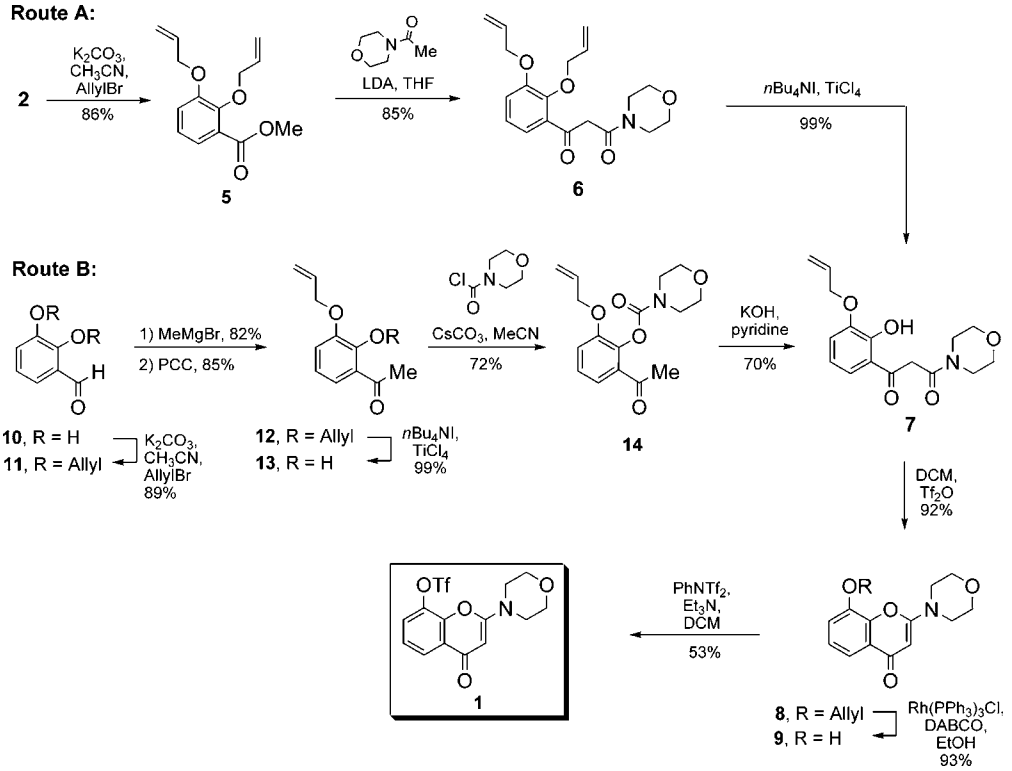
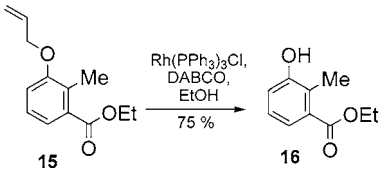
Scheme 2. Synthesis of Triflate **1** from Ester **5**[a] or Aldehyde **10**[b]



[a] 35% overall yield. [b]15% overall yield.

Comparison of the three methods described for the synthesis of triflate **1** shows that the published method[4] has the advantage of being the shortest (three steps) but has an unacceptable, very poor overall yield of just 4%. The Baker–Venkataraman route gave acceptable yields throughout over nine straightforward steps, affording **1** in 15% overall yield. Modification of the original route[4] by judicious protection–deprotection of hydroxyl groups with allyl represented a significant improvement in overall yield (35%). The three extra steps required were all trivial and high yielding.

Scheme 3. Rh-Mediated Deprotection of **15**



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Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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