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Application of Isayama–Mukaiyama cobalt catalyzed hydroperoxysilylation for the preparation of ritonavir hydroperoxide

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ABSTRACT

We report the preparation of thiazol-5-ylmethyl ((2*S*,3*S*,5*S*)-5-((*S*)-2-(3-((2-(2-hydroperoxypropan-2-yl) thiazol-4-yl)methyl)-3-methylureido)-3-methylbutanamido)-3-hydroxy-1,6-diphenylhexan-2-yl)carbamate, a hydroperoxide impurity of ritonavir also known as ritonavir USP impurity G. Due to the complexity of ritonavir's structure and abundance of oxidation susceptible functional groups, forced degradation was found to be a non-selective and inadequate tactic. Therefore, a multistep synthesis was applied. The overall strategy involved initial introduction of a propenyl moiety to the terminal thiazole which enabled selective oxidation using $Co(thd)_2$ (0.1 equiv)/O_2 (Isayama–Mukaiyama cobalt catalyzed hydroperoxysilylation) following structural assembly.

Introduction

Ritonavir is an HIV aspartic protease inhibitor and potent Cytochrome P450 (CYP) inhibitor which is used in the clinic as part of fixed dose combinations mostly due to its CYP inhibitory effect. Inhibition of CYPs assists in elevating blood levels of other HIV inhibitors introduced in fixed combination products.[1,2]

Impurities in drugs are of major concern in terms of quality and safety. Example impurity sources are remnants of starting materials, intermediates, and reagents from the synthesis of the active pharmaceutical ingredient (API), degradation of the API,[3] and reaction of the API with excipients[4] or their contaminants.[5]

In order to be able to identify, quantify and to assess their toxicity potential, impurity standards and markers are required. Nevertheless, they are not always commercially available and there is a continuous pursuit for new sources.

On many occasions, preparation, isolation, and characterization are possible simply by applying the same conditions that led to the formation of the desired impurity (forced degradation). However, in some circumstances, forced degradation is not possible or not effective. In many cases, impurities form only in formulated low dosage drug products (approximately 1 mg per dose) and exhaustive preparative isolation is not practical. In some cases, there is a need for toxicological studies or testing in the Ames assay. In these instances, a considerable amount (multigram) of the impurity is required and is not always available by implementation of non-selective, low yielding forced degradation. An additional obstacle is met when forced degradation is not able to replicate the slow constant degradation pathway that an API undergoes in a given formulation during long periods of storage. In other occasions, the molecule contains several functional groups which are sensitive to the applied conditions. For example, molecules such as dabigatran etexilate[6], sofosbuvir,[7] and tenofovir disoproxyl[8] comprise more than one reactive site which can be cleaved by simple hydrolytic conditions.

When forced degradation is not effective, there is a need for synthesis of the desired impurity. Herein, we describe the preparation of ritonavir hydroperoxide. Although this compound is known and defined in the USP, a literature search, including SciFinder, did not reveal any published total synthesis.

Results and discussion

Initial attempts at forced degradation synthesis focused on the base promoted oxidation of ritonavir. It was reasoned that the methine hydrogen of the isopropyl group adjacent to the 2-thiazole group might be sufficiently labile to enable deprotonation and subsequent functionalization under an oxygen atmosphere.[9,10] Ritonavir was treated with excess KO*t*-Bu (5 equiv) under an oxygen atmosphere in THF at room temperature (Scheme 1). However, this first attempt resulted in rapid intramolecular cyclization of

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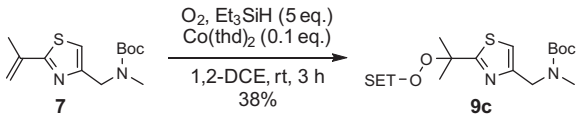
ritonavir to form oxazolidone derivative **2**. To eliminate the possibility of cyclization, the 3-hydroxyl group of ritonavir was first protected as *tert*-butyldimethylsilyl ether derivative **3** under standard conditions in 72% yield. This substrate was subjected to the KO*t*-Bu/O_2 degradation conditions in both THF and DMF at temperatures ranging from room temperature to 60 °C. Unfortunately these conditions produced only complex reaction mixtures with no clearly isolable hydroperoxide product.

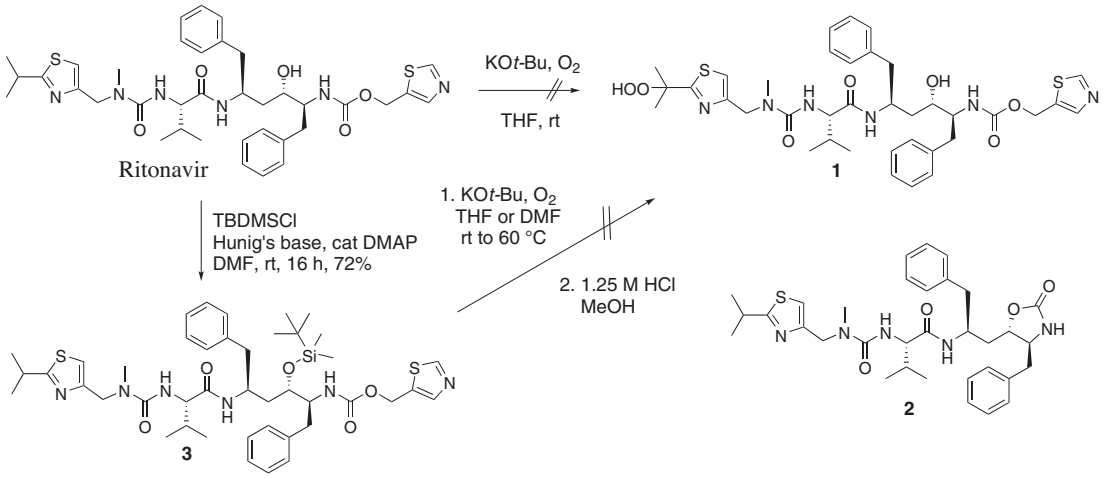
With the failure of the direct degradation of ritonavir, we turned our attention to a total synthesis approach and targeted the peroxidation of a simplified 2-isopropylthiazole fragment which could be used as a key intermediate in the synthesis of **1**. Boc-protected intermediate **8** (Scheme 2) appeared to be a suitable substrate to apply the base promoted oxygenation reaction since it lacked the protic functional group present in ritonavir. Compound **8** was synthesized from commercially available 2-bromothiazole-4-carbaldehyde **4** in four steps. Reductive amination followed by Boc-protection afforded 2-bromothiazole derivative **6** in 62% overall yield. The key step to introduce the isopropyl group utilized a Suzuki reaction to first synthesize the isopropylene derivative **7** in 68% yield, which was subsequently hydrogenated to afford **8** in 56% yield.

Compound **8** was subjected to the base promoted oxidation protocol using KOtBu/O_2 in various solvents (THF, *tert*-butanol, and DMF) at room temperature. THF and *tert*-butanol gave poor results with only trace amounts of **9a** observed by LCMS along with other unidentified side-products. The use of DMF afforded an improved conversion, however, attempts to isolate **9a** by reverse phase chromatography yielded only trace quantities of the product. In order to facilitate isolation of the peroxide, a stepwise *O*-silyl protection method was employed. Addition of TBDMSCl to the reaction mixture after 2 h formed the *O*-*tert*-butyldimethylsilyl peroxide **9b** which was isolated by reverse phase chromatography in 19% yield. Attempts to increase the yield of **9b** by elevating the reaction temperature to 60 °C in the oxidation step resulted in a complex reaction mixture and decomposition of **9a**. Limited by the low yield of the base promoted oxidation, we considered alternative oxidative methods.

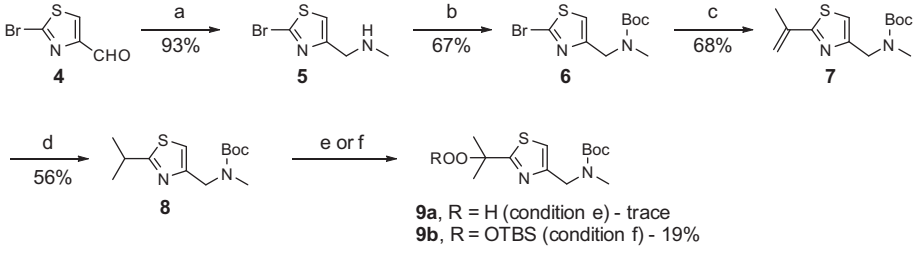
The cobalt catalyzed hydroperoxysilylation of alkenes, first reported by Isayama and Mukaiyama,[9] represents a convenient and mild procedure for the regioselective conversion of alkenes into the corresponding triethylsilylperoxide derivatives in good yields. This protocol has been utilized in the synthesis of various peroxide derivatives[11] and peroxide containing natural products.[12–14] It was considered that 2-isopropylene-thiazole intermediate **7** might serve as a suitable substrate for catalyzed hydroperoxysilylation and given the success in isolating *O*-silyl derivative **9b**, this approach appeared appealing. A trial reaction of α-methylstyrene using $Co(accac)_2$ (0.1 equiv), O_2 (1 atm.), and triethylsilane (1.0 equiv), for 3 h at room temperature in 1,2-dichloroethane afforded the expected OTES-protected tertiary hydroperoxide in 82% yield after chromatography. However, initial application of these conditions to intermediate **7** failed to afford the desired peroxide **9c** even after a prolonged reaction time of



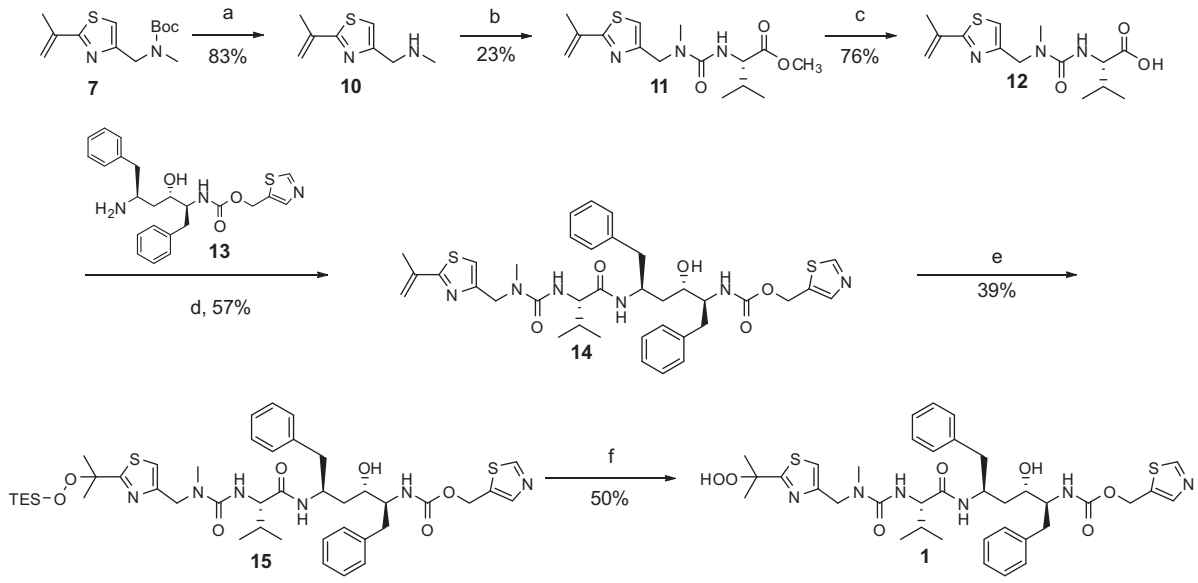
Scheme 3. Cobalt catalyzed OTES peroxidation of **7**.



Scheme 1. Attempted base promoted forced degradation of ritonavir.



Scheme 2. Synthesis of intermediate **8**. Reagents and conditions: (a) (i) CH_3NH_2 (33% in EtOH), $Ti(OiPr)_4$, rt, 16 h (ii) $NaBH_4$, rt, 4 h; (b) Boc_2O, Et_3N, CH_2Cl_2, rt, 8 h; (c) 4,4,5,5-tetramethyl-2-(prop-1-en-2-yl)-1,3,2-dioxaborolane, 2M $NaHCO_3$, DMF, 90 °C, 4 h; (d) H_2 (1 atm), Pd/C (10 wt%), MeOH, rt, 8 h; (e) KO*t*Bu, O_2, rt, 2 h; (f) (i) KO*t*Bu, O_2, rt, 2 h, (ii) TBDMSCl, rt, 3 h. Note: all yields are unoptimized.



Scheme 4. Synthesis of **1**. Reagents and conditions. (a) 4 M HCl in 1,4-dioxane; (b) (i) triphosgene, Hünig's base, THF, −10 °C, 2 h (ii) *N*-Val-OCH_3, Hünig's base, THF, −10 °C to rt, 2 h; (c) 2M NaOH, MeOH, rt, 4 h; (d) EDCI, HOBt, Hünig's base, DMF, rt, 16 h; (e) $Co(thd)_2$ (0.1 equiv), O_2 (1 atm.), Et_3SiH (5 equiv), 1,2-DCE, rt, 30 h; (f) 0.05% TFA(aq.), rt, 2 h. Note: yields are unoptimized.

16 h. Subsequently, small modifications were made to the reaction conditions, firstly changing the cobalt complex to the more sterically hindered bis(2,2,6,6-tetramethyl-3,5-heptanedionato)cobalt (II) $Co(thd)_2$ which has been reported as a superior catalyst for the transformation.[15] Upon substituting this catalyst in place of $Co(accac)_2$, we were disappointed to see no improvement in the conversion of **7** to **9c**. The effect of the stoichiometry of the triethylsilane reductant was examined, showing that employing an excess of triethylsilane reductant had a significant benefit to the reaction yield. Using the modified conditions of $Co(thd)_2$ (0.1 equiv), O_2 (1 atm.), and triethylsilane (5.0 equiv) in 1,2-dichloroethane for 3 h at room temperature afforded **9c** in 38% isolated yield (Scheme 3).

This result confirmed that the Isayama–Mukaiyama peroxidation could be utilized for heterocyclic substrates such as **7**. Moreover, the TES-group served the added utility as a protecting group for the presumably chemically sensitive hydroperoxide. Despite this we doubted the ability of the OTES group to remain intact during the subsequent transformations required to synthesize the final product **1**. To increase the chances of success, we postulated that the critical hydroperoxysilylation step might be performed at a later stage in the synthesis, ideally as the penultimate step (Scheme 4). The key intermediate for this approach was the isopropenyl derivative of ritonavir, compound **14**. The overall synthetic strategy toward **14** involved transformation of isopropenyl intermediate **7** to valine derivative **12** and subsequent peptide coupling with amine fragment **13**. Compound **7** was subjected to Boc deprotection to afford free amine **10** in high yield. Initial attempts to convert **10** to urea derivative **11** utilizing CDI/DBU conditions failed. Eventually compound **10** was converted to the *N*-carbamoyl chloride derivative by treatment with triphosgene/Hünig's base followed by in situ coupling to L-valine methyl ester to afford **11** in modest yield. Ester hydrolysis afforded carboxylic acid **12** which was coupled with amine **13** under standard EDCI/HOBt conditions to afford the desired oxidation precursor **14**. In the critical step compound **14** was successfully converted to OTES-peroxide derivative **15** using the modified hydroperoxysilylation in 39% isolated yield. Final removal of the OTES group was achieved under mildly acidic conditions using 0.05% aqueous TFA. The crude hydroperoxide was purified by reverse chromatography to afford **1** in 50% yield.

Conclusion

A concise and practical synthesis of a ritonavir-hydroperoxide derivative **1** has been developed. The synthesis employs a late stage application of the Isayama–Mukaiyama cobalt catalyzed hydroperoxysilylation reaction to an alkene derivative of ritonavir and demonstrates the utility of the reaction for the synthesis of complex hydroperoxide containing products. A crucial modification to the reaction conditions involved the use of excess triethylsilane reductant, which appeared to be beneficial to enable the transformation to be carried out in the presence of heterocycles and complex structural functional groups.

Supplementary data

Supplementary data (synthetic procedures, characterization data, copies of ESI-MS data and ^1H NMR spectrum of products) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.10.022.

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