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PII: S0040-4039(17)30564-6
DOI: http://dx.doi.org/10.1016/j.tetlet.2017.05.001
Reference: TETL 48894

To appear in: *Tetrahedron Letters*

Received Date: 4 April 2017
Revised Date: 28 April 2017
Accepted Date: 1 May 2017

Please cite this article as: Jeong, J.U., Harris, P.A., Kang, J., Leister, L., Lan, Y., Romano, J., Dong, X., Marquis, R.W., Synthesis of (*S*)-3-Amino-benzo[b][1,4]oxazepin-4-one via Mitsunobu and S_NAr Reaction for a First-in-Class RIP1 Kinase Inhibitor GSK2982772 in Clinical Trials, *Tetrahedron Letters* (2017), doi: http://dx.doi.org/10.1016/j.tetlet.2017.05.001

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

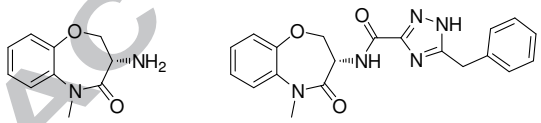
Keywords:
RIP1 kinase inhibitor
Benzo[b][1,4]oxazepin-4-one
Mitsunobu
S_NAr cyclization

ABSTRACT

Two new synthetic routes were developed to prepare the RIP1 kinase inhibitor clinical candidate GSK2982772 involving a key (*S*)-3-amino-benzo[b][1,4]oxazepin-4-one intermediate prepared via Mitsunobu and S_NAr cyclization reactions. Both routes are practical and cost effective compared to the initial medicinal chemistry route and are also applicable to kilogram scale-up to support on-going clinical studies.

Introduction

Receptor interacting protein 1 (RIP1) kinase has recently emerged as a promising therapeutic target for the treatment of multiple inflammatory diseases in TNF-mediated inflammation.[1-4] During our drug discovery efforts, (*S*)-3-amino-benzo[b][1,4]oxazepin-4-one (**1**) (Figure 1) was identified as an important pharmacophore as part of a RIP1 kinase inhibitor series.[5] This benzoxazepinone template **1** has also been employed to treat other biological targets like β-secretase,[6] angiotensin converting enzyme (ACE)[7] and inhibitor of apoptosis proteins (IAPs).[8]



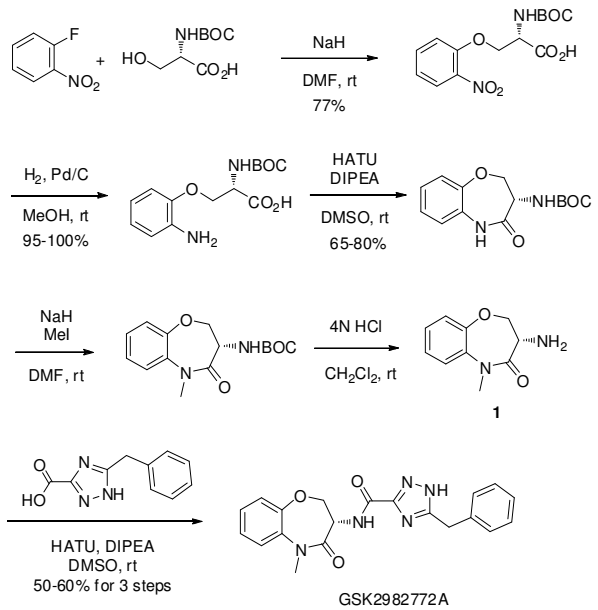
1

GSK2982772

IC_{50} = 1.0 nM in ADP-Glo enzyme assay
IC_{50} = 6.3 nM in U937 cellular assay
Oral AUC: rat 2.3, monkey 2.9 µg.h/mL
Oral bioavailability: rat 110, monkey 86 %

Figure 1. Structures of benzoxazepinone **1** and GSK2982772

Lead optimization of this series led to identification of GSK2982772 (Figure 1), a first-in-class RIP1 kinase inhibitor currently undergoing phase 2 clinical trials for the treatment of psoriasis, ulcerative colitis and rheumatoid arthritis.[9] GSK2982772 possesses high in vitro potency and excellent kinase selectivity, which combined with has highly favorable physicochemical and pharmacokinetic properties makes this a highly attractive development candidate.



Scheme 1. The initial route to synthesize GSK2982772

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The initial route for the synthesis of GSK2982772 required 6 steps (not including the preparation of triazole carboxylic acid), which was described previously starting from 1-fluoro-2-nitrobenzene and Boc-L-serine as shown in Scheme 1.[5,9] This chemistry could be successfully scaled-up up to the kilogram scale, but we decided to fully evaluate different synthetic routes to the key intermediate **1**. Any viable alternative synthesis had to be as efficient and cost effective compared to the initial synthesis (6 steps to GSK2982772 and good overall yields).

Herein, we report two new efficient synthetic routes using different and readily available starting materials, with no overlapping steps with the initial synthesis. Our new approaches utilizing the Mitsunobu reaction and the S_NAr reaction for intramolecular ether formation to prepare the 7-membered ring looked promising as illustrated in Figure 2. Both routes used different starting materials compared to the initial synthesis. Neither route required the reduction of aryl nitro group which was achieved in the initial synthesis (Scheme 1) using palladium on carbon, but provided significant undesired color contamination.

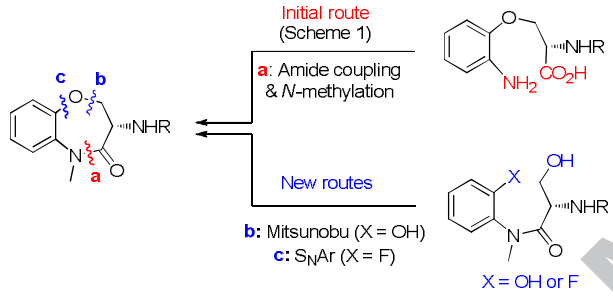
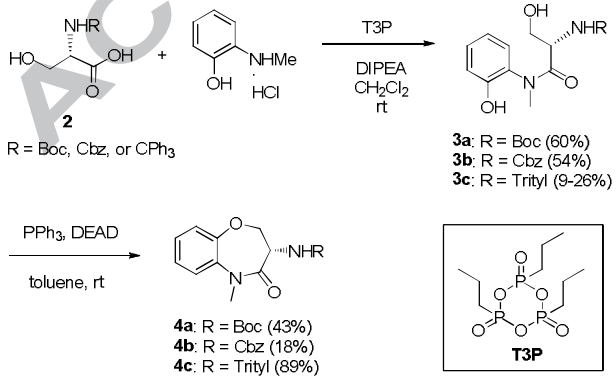


Figure 2. 7-Membered ring formation for benzoxazepinone

Results and Discussion

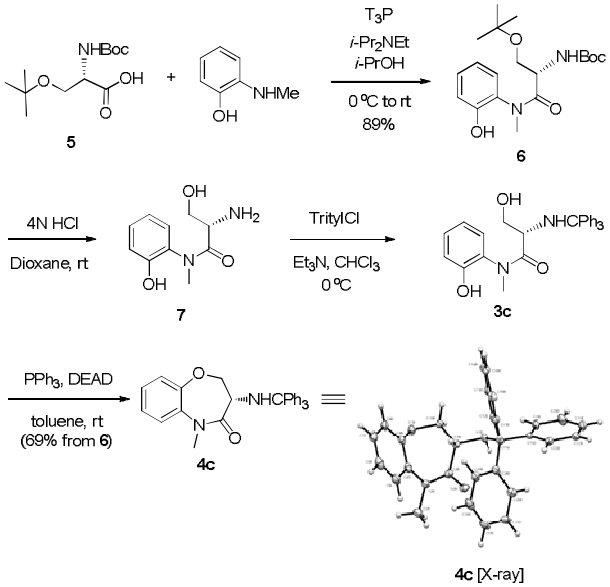
The key Mitsunobu cyclization using the standard conditions[10] was evaluated as shown in Scheme 2. Various protected L-serines **2** were coupled with 2-(methylamino)phenol using the commercially available and efficient coupling reagent for the epimerization-prone substrates, T3P (*n*-propanephosphonic acid anhydride)[11] and *i*-Pr_2NEt, followed by Mitsunobu cyclization using PPh_3 and DEAD to yield the cyclized products **4a-c**.



Scheme 2. Initial attempts via Mitsunobu reaction

Employing either Boc or Cbz protected serine the coupling step was good (54-60% yield), but the yield for the subsequent Mitsunobu cyclization was poor (18-43% yield). To optimize the cyclization we switched to the trityl protecting group, which increased the steric bulk to promote cyclization due to the angle compression similar to the Thorpe-Ingold effect[12] as well as reduced the acidity of the NH proton to reduce potential side reactions. This resulted in substantially increasing the yield of the Mitsunobu cyclization step (**3c** to **4c**) to 89%. However, the major disadvantage using the trityl protecting group was that the initial coupling step with trityl-L-serine became low yielding (9-26%).

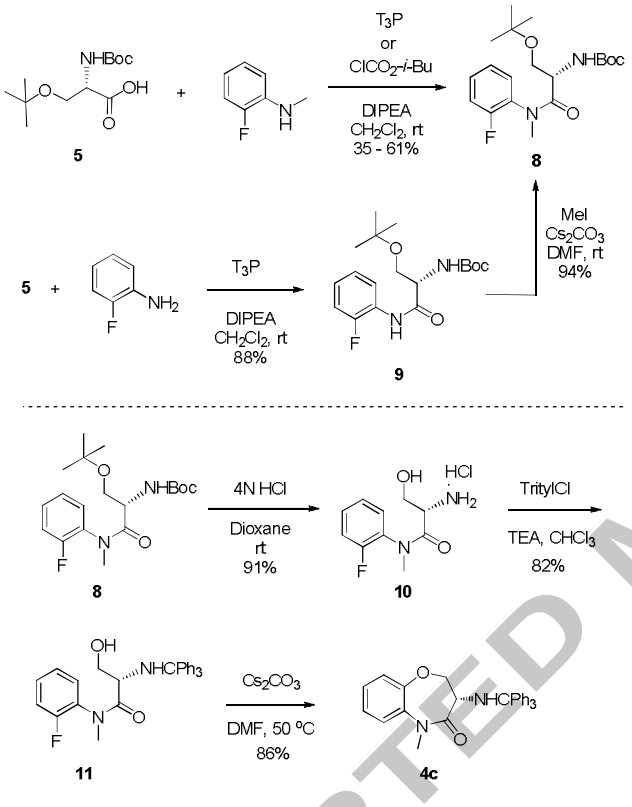
After extensive optimization, the preferred Mitsunobu route started with readily available (*S*)-3-(*tert*-butoxy)-2-((*tert*-butoxycarbonyl)amino)propanoic acid **5** as a fully protected starting material to improve yield for the amide coupling reaction. It was coupled with 2-(methylamino)phenol using T3P and *i*-Pr_2NEt to provide the coupling product **6** in high yield (89%). Both protecting groups of **6** were simultaneously removed using acidic conditions (4M HCl in dioxane) and the resulting free amine **7** was protected with the optimal trityl protecting group. Without any further purification, the trityl protected amine **3c** was cyclized to the desired product **4c** via Mitsunobu reaction using PPh_3 and DEAD with good isolated yield (69% for 3 steps from intermediate **6**). The structure was also confirmed by a small molecule x-ray structure as shown in Scheme 3. Although this optimized route requires two additional steps to manipulate the proper protecting groups, the overall yield is much better than initial attempts using the Mitsunobu cyclization as shown in Scheme 2 and the number of steps is comparable with the initial route we were aiming to replace.



Scheme 3. New synthetic route via Mitsunobu reaction

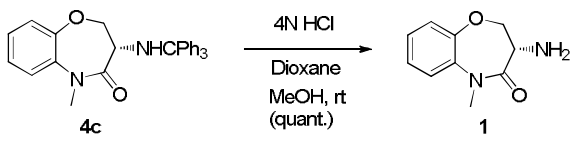
A second alternative approach we studied to prepare **1** involved a nucleophilic aromatic substitution (S_NAr) cyclization as shown in Scheme 4. The precursor **8** for the S_NAr reaction was initially prepared from the fully protected serine **5** and 2-fluoro-*N*-methylaniline in one step using T3P or *i*-butyl chloroformate, but the reaction was sluggish in general and provided moderate yields (35-61%). Instead, the precursor **8** was prepared in 2 steps

with better yield from the coupling reaction (88%) using 2-fluoroaniline with T3P and *i*-Pr_2NEt, followed by *N*-methylation (94%) of **9** using methyl iodide. Although this added an additional methylation step, these conditions were practical and worked well on a large scale. After removal of both protecting groups with acidic conditions (4M HCl in dioxane), the resulting free amine **10** was protected with the optimal trityl protecting group similar to the previous reactions shown in Scheme 3. The trityl protected amine **11** was successfully cyclized to the cyclized product **4c** in high yield (86%) using Cs_2CO_3 in DMF at 50 °C.



Scheme 4. New synthetic route via S_NAr cyclization

Finally, the key amino benzoxazepinone, (*S*)-3-amino-benzo[b][1,4]oxazepin-4-one (**1**), was obtained from **4c** after deprotection using an acidic condition (4M HCl in dioxane) as shown in Scheme 5, which was identical to the compound **1** using the initial route summarized in Scheme 1. This key amino benzoxazepinone **1** was coupled with triazole carboxylic acid using coupling agents such as HATU and T3P to complete the synthesis of GSK2982772.[9,13]



Scheme 5. Final step for the benzoxazepinone core 1

In conclusion, two new synthetic routes to prepare the amino benzoxazepinone core **1** were successfully developed. Both routes are viable alternatives to the initial route, have similar cost-of-good analysis and are applicable for the scale up of GSK2982772. The S_NAr cyclization route was successfully applied to prepare >5 kilogram batches of API. Further details for the application of both routes will be reported in due course.

Acknowledgments

The authors thank Minghui Wang and Grazyna Graczyk-Millbrandt for their assistance with full characterization of key compounds by NMRs.

A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/xxxxx

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13. The chiral purity of GSK2982772 was determined with the following method: Chiral HPLC analysis using a Lux Cell 4 analytical column (150 mm × 4.6 mm), eluting with 10:90 MeOH:CH_3CN plus 0.1% isopropylamine as the mobile phase at flow rate 1 mL/min, provided good separation of a racemic standard. The desired S enantiomer GSK2982772 eluted at 3.99 min. The separately prepared R enantiomer (not shown) eluted at 7.16 min. This indicated that the chiral purity of GSK2982772 prepared from the key intermediate **1** via the Mitsunobu reaction and the S_NAr reaction was >99.9% ee, with none of the R enantiomer detected.

Graphical Abstract

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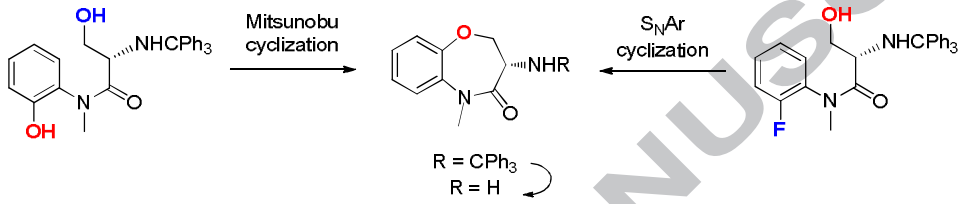

Two new synthetic routes were developed to prepare the RIP1 inhibitor clinical candidate GSK2982772 involving a key (*S*)-3-amino-benzo[b][1,4]oxazepin-4-one intermediate prepared via Mitsunobu and S_NAr cyclization reactions. Both routes are practical and cost effective compared to the initial medicinal chemistry route and are also applicable to kilogram scale-up to support on-going clinical studies.

Highlights

- Two new synthetic routes to 3-amino-benxoxazepin-4-one were developed.
- Successful optimization for Mitsunobu and S_NAr cyclization reactions.
- Efficient and practical synthesis applicaple to kilogram scale-up.