Organic Chemistry: An Indian Journal

Organic Chemistry
ISSN: 0974-7516

Short Communication | Vol 16 Iss 1

A Progressive C-H Functionalization Technique Was Used to Complete the Whole Synthesis of K-252c

Darrin Jones*

Editorial office, Trade Science Inc., UK

***Corresponding author:** Darrin Jones, Editorial office, Trade Science Inc., UK, E-mail: organicchem@journalres.com
Received: January 05, 2022; **Accepted:** January 15, 2022; **Published:** January 25, 2022

Introduction

A progressive C-H functionalisation approach was used to synthesise the bioactive indolocarbazole alkaloid K-252c (staurosporinone). The route uses direct functionalisation reactions around a simple arene core and includes two highly selective copper-catalyzed C-H arylations, a copper-catalyzed C-H amination, and a palladium-catalyzed C-H carbonylation, all of which contribute to the natural product framework's structural complexity. The indolocarbazole alkaloids have piqued the synthetic community's interest due to their fascinating biological features and potential as medicinal agents. K-252c, has garnered a number of elegant syntheses as a putative biosynthetic precursor and aglycone of staurosporine. The distinctive functional structure of the hexasubstituted arene framework drew us to these natural compounds because of their intriguing biological activity.

Our research has long been fascinated by natural product synthesis methods that rely on the successive functionalisation of C-H bonds in simple aromatic building blocks. We thought K-252c could be used to extend this entire synthesis technique by coordinating a series of direct functionalisations on a conveniently available aniline to generate the target molecule's fully substituted benzene core Furthermore, such a modular strategy would be amenable to the preparation of analogues of this important scaffold. Herein we report a concise synthesis of the indolocarbazole alkaloid K-252c starting from a commercial toluidine starting material. Seven direct functionalisations are used to transform C-H bonds of the aniline into the substituents required for the hexasubstituted arene core of the natural product architecture. Despite the increasingly complex architecture that results from each step, a notable feature of this synthesis is the exquisite selectivity of each C-H transformation, thereby highlighting the efficacy of sequential C-H functionalisation strategies. The work of Wood and colleagues, who devised a simple method to this class of natural compounds, is the most elegant of these syntheses. Despite the ease of this form of strategic disconnection, engineering an unsymmetrical indolocarbazole framework from such a convergent route remains tough. We hypothesised that a sequential C-H functionalisation technique could benefit from late-stage carbazole formations to modify the electron density of the central arene core as part of our synthetic strategy for staurosporinone. The lactam would be produced by a C-H carbonylation controlled by the benzylamine motif, which may be added by radical-mediated benzylic oxidation. These disconnections would disclose a teraryl framework with an amine motif that would regulate the selective installation of the next nitro group, as well as a succession of ortho- and meta-C-H arylations that would lead back to p-toluidine. The aniline's amine motif regulates four of the seven direct functionalisations on the aromatic framework of this complicated molecule when taken collectively. The limited reactivity of the product to subsequent arylations, we believe, is responsible for the process' selectivity. The amino group rotates out of conjugation with the arene as a result of a conflict between the ortho-phenyl substituent and the N,N-dibenzyl group, lowering the arene nucleophilicity and making it less reactive towards a second arylation.

Citation: Ward S. A Progressive C-H Functionalization Technique Was Used to Complete the Whole Synthesis of K-252c. Org Chem Ind J. 2022;16(1):62

We wondered if p-toluidine, a common commercial aniline, could be utilised to start a sequential C-H functionalisation strategy for the synthesis of K-252c at the start of our design stage. The indolocarbazole framework is assembled by joining two indole molecules with a synthetic precursor to the lactam ring system, followed by an oxidative electrocyclization to generate the poly(hetero)aromatic framework in many of the prior syntheses. The phrase recycling is a broad term with many different connotations depending on the year and author. Plastics manufacturers have also issued their own set of rules nicknamed Design for Recycling. According to a widely accepted notion of plastic recycling, "the method of reclaiming scrap or waste plastics and reprocessing the material into useful objects, frequently radically different in shape from their initial state." Breaking down techniques by recycled polymer, finished product, or process distinguishes them even more, which can lead to inconsistencies and overlaps.

We planned to employ a copper-catalyzed meta-arylation, which was also recently created in our lab, to install the second aryl group. However, in order to do this, the N-benzyl substituents have to be replaced with a carbonyl-containing group, which is necessary for the meta-selective arylation to occur. The composition of the carbonyl group had to be carefully evaluated in terms of its efficacy in the meta-arylation, its stability under following reaction conditions, and compatibility with the oxidative C-H amination that would be required later in the synthesis to generate the carbazole. We previously demonstrated that a pivalamide group is the most effective for meta-arylation, however there are no examples of C-H aminations employing amines generated with this bulky group. Due to competitive amide cleavage, meta-arylation driven by simple acetamides was generally low yielding, despite the fact that this simple amide motif can launch a number of C-H aminations. We chose the propionyl group to explore in order to see if the increased size of the ethyl substituent would make the amide less prone to cleavage while still being efficient in the carbazole production phase. On a multi-gram scale, a one-pot hydrogenolysis followed by carbamoylation with propionyl chloride enabled the synthesis of anilide in outstanding 96 percent yield. On a 4 g scale, treatment of anilide 9 with diphenyliodonium triflate in the presence of copper(i) iodide, silver(i) triflate (providing an in situ source of copper(i) triflate), and solid sodium hydrogen carbonate (to buffer the reaction in light of the formation of triflic acid as a by-product) produced the teraryl intermediate 10 in 71 percent yield.

After obtaining teraryl, the next step was to add the second nitrogen substituent. The installation of a nitro group, which could then be used in a late-stage reductive cyclisation to a carbazole, was thought to be the best option. Although attempts to scale-up the reaction were unsuccessful, resulting in lower yields, treatment of 10 with concentrated nitric acid in a cooled solution of trifluoroacetic anhydride and trifluoroacetic acid provided the desired product in 60% yield. Several metal catalysed C-H aminations to carbazoles have been established in recent years, however when applied to our system, we discovered that palladium-catalyzed carbazole production methods were either capricious or produced no of the desired product. While we reasoned that reductive amination of aldehyde with a suitable amine would yield a precursor for the suggested C-H carbonylation to generate the -lactam, we were aware that primary amines have high coordination to metals like palladium and frequently impede catalytic activity. As a result, we chose to use a benzylic amine for the reductive amination with the goal of applying Orito's C-H carbonylation to the required protected -lactam. However, the choice of amine required more thought, as using benzyl amine would cause selectivity issues in the C-H carbonylation's carbopalladation phase. Keeping this in mind, we created a series of benzylamine variations with ortho-substituents to prevent competitive C-H activation.

Conclusion

In conclusion, we were able to successfully synthesise K-252c using a sequential C-H bond functionalisation approach. When using a widely accessible aniline, the overall yield is 12.7%. The amine group of the beginning toluidine controls four of the C-H functionalisations, therefore the series of direct functionalisations follows a logical order of reactivity. Two selective copper-catalyzed C-H arylations, a very selective electrophilic nitration, two C-H amination protocols

Citation: Ward S. A Progressive C-H Functionalization Technique Was Used to Complete the Whole Synthesis of K-252c. Org Chem Ind J. 2022;16(1):62

to generate carbazoles, a benzylic methyl oxidation, and a palladium-catalyzed C-H carbonylation are among the transformations featured in the synthesis. Scaling up the synthesis allows for access to intermediates on a gramme or multigram scale. This modular technique might also be utilised to enable quick access to analogues of this biologically significant type of chemical, as well as complex hexasubstituted benzenes. Our lab's current research focuses on using this sequential C-H functionalisation technique to synthesise staurosporinone analogues and other complicated natural compounds that could benefit from it.

References

1. Burange AS, Gawande MB, Lam FL, et al. Heterogeneously catalyzed strategies for the deconstruction of high density polyethylene: plastic waste valorisation to fuels. Green Chem. 2015;17(1):146-56.
   Google Scholar Crossref
2. Kaur G, Uisan K, Ong KL, et al. Recent trends in green and sustainable chemistry & waste valorisation: rethinking plastics in a circular economy. Curr Opin Green Sustain Chem. 2018;9(1):30-9.
   Google Scholar Crossref
3. Liguori F, Moreno-Marrodán C, Barbaro P. Valorisation of plastic waste via metal-catalysed depolymerisation. Beilstein J Org Chem. 2021;17(1):589-621.
   Google Scholar Crossrefs

Citation: Ward S. A Progressive C-H Functionalization Technique Was Used to Complete the Whole Synthesis of K-252c. Org Chem Ind J. 2022;16(1):62