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Synthesis of Thienoisoquinolines WITH Palladium-Catalyzed Cross-Coupling

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Abstract – Thienoisoquinolines are biotically animated heterocyclic frameworks that have potential as a breast tumor restorative. Advancements and amalgamations of functionalized thienoisoquinolines from industrially ready beginning material are depicted. The amalgamations location regular restrictions connected with established palladium cross-coupling responses for example the utilization of touchy organometallic reagents and the processing of towering atomic weight metallic waste.

The crux transitional was blended in 2 steps from a financially ready beginning material and utilized within two manufactured pathways to gain entrance to distinctive thienoisoquinoline isomers. Experiencing a palladium catalyzed twofold C-H initiation response permits access to the 3,4-thienoisoquinoline isomer . The ester practicality at C2 serves a double reason and was utilized both as a running gathering and as a manufactured handle for further functionalization.

The nexus middle of the road can moreover experience a saponification response first to shape the carboxylic harsh corrosive. This takes into account a palladium catalyzed decarboxylative cross-coupling, producing 2,3-thienoisoquinoline frameworks. This might be further functionalized at the C5 position through a C-H actuation or bromination response. Besides, the aforementioned functionalized 2,3-thienoisoquinoline frameworks could be incorporated through an one-pot decarboxylative cross-coupling & C-H initiation arrangement decreasing the step check and enhancing proficiency. In summation, a powerful amalgamation of different functionalized thienoisoquinoline frameworks is portrayed. Both isomers of the aforementioned biotically significant combines might be gotten from a normal key moderate taking into account an effective and secluded combination.

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INTRODUCTION

In the not so distant future Nobel Prize in Chemistry concerns the improvement of routines for palladium-catalyzed establishment of carbon-carbon bonds by means of supposed cross-coupling reactions. The arrangement of new carbon-carbon bonds is of centermost criticalness in natural science and an essential for all life on earth. Through the get together of carbon molecules into chains, complex particles, e.g. particles of life, could be made. The significance of the amalgamation of carbon-carbon bonds is reflected by the way that Nobel Prizes in Chemistry have beforehand been given to this range: The Grignard response (1912), the Diels-Alder response (1950), the Wittig response (1979), and olefin metathesis to Y. Chauvin, R. H. Grubbs, and R. R. Schrock (2005).

Move metals in manufactured natural science : During the second a large part of the 20th century, move metals have come to play a paramount part in natural science and this has prompted the advancement of an impressive number of move metal-catalyzed reactions for making natural atoms. Move metals have a novel capability to enact different natural fuses and through this initiation they can catalyze the shaping of new bonds. One metal that was utilized right off the bat for reactant natural conversions was palladium. One occasion that animated research into the utilization of palladium in natural science was the revelation that ethylene is oxidized to acetaldehyde via air in a palladium-catalyzed response and this ended up being the modernly imperative Wacker process.1 Subsequent explore on palladium-catalyzed carbonylation accelerated new reactions for the development of carbon-carbon securities. By and large, move metals, and specifically palladium, have been of vitality for the improvement of reactions for the structuring of carbon-carbon bonds. In 2005 the Nobel Prize in science was recompensed to metal-catalyzed reactions for the creation of carbon-carbon twofold bonds. In the not so distant future the Nobel Prize in science is granted to the development of carbon-carbon single bonds through palladium-catalyzed cross-coupling reactions.

Palladium-catalyzed carbon-carbon bond structuring by means of cross coupling : The rule of palladium-catalyzed cross couplings is that two particles are gathered on the metal through the structuring of metal-carbon bonds. Thusly the carbon particles bound to palladium are carried exceptionally near each other. In the following step they couple to each other and this expedites the framing of another carbon-carbon single bond.

PALLADIUM CROSS-COUPLING

Carbon-carbon bonds have dependably had an essential effect on the field of manufactured natural science in the infrastructure of new techniques, characteristic feature amalgamation and medicinal science. All the more as of late, move metal catalyzed carbon-carbon security shaping reactions have been built as an elective to traditional systems to create the aforementioned bonds. To show the essentialness of the aforementioned reactions in the advancement of therapeutics, an investigation of the reactions utilized by GlaxoSmithKline pharmaceuticals, AstraZeneca and Pfizer in the amalgamation of 128 pill petitioners was performed via Carey and work mates in 2006.

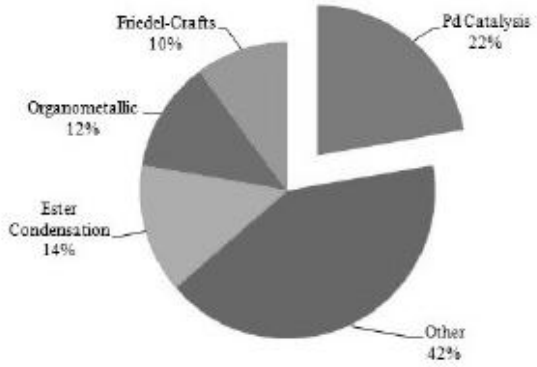
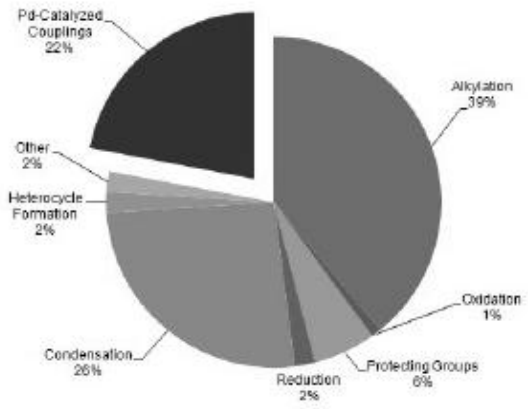


Figure – Breakdown of C-C bond forming reactions

Any time ordering the sum of the reactions performed, 11% of the reactions were carbon-carbon bond shaping. Further dissection of this set of reactions uncovered that 22% of the aforementioned carbon-carbon bond framing reactions were palladium catalyzed .

To further stress the criticalness of palladium catalyzed carbon-carbon bond shaping reactions, a second study was performed by Cooper and work mates at GlaxoSmithKline. This study overviewed reactions utilized towards the combination of clinical applicants for respiratory infections.



Figure– Survey of reactions used at GlaxoSmithKline towards respiratory disease clinical candidates.

Cooper likewise discovered that 22% of the reactions performed were palladium-catalyzed, which exhibited the essentialness of the aforementioned changes. The two studies performed enveloped the amalgamation of diverse therapeutics for distinctive malady ranges, further showing the flexibility and pertinence of palladium-catalysis in medication disclosure.

This class of reactions might be characterized into two assemblies; traditional strategies and present day routines. Established systems are made out of changes for example the Suzuki, Hiyama, Negishi, Stille and Kumada reactions that utilized the utilization of an organometallic species coupling with an aryl halide. The aforementioned reactions expedited and enhanced the amalgamation of the aryl aryl bond. These cross-coupling reactions are chemioselective with aryl halides or oxygen-based leaving assemblies, generally reputed to be pseudo halides, and the relating organometallic aggregation. The aforementioned reactions likewise are ordinarily tolerant of other practical aggregations, along these lines taking into account expansive pertinence with a mixture of substrates.

SYNTHESIS OF 3,4-THIENOISOQUINOLINES

A survey of the literature revealed only a single synthesis of these important compounds reported by Bogza and co-workers in 2009. However, the reported synthesis was specific for a single 3,4-thienoisoquinoline system and not designed for library synthesis. Furthermore, the synthesis required the use of harsh acidic conditions to facilitate cyclization. Therefore, the application of this method on an industrial scale or for small molecule inhibitor development was not ideal.

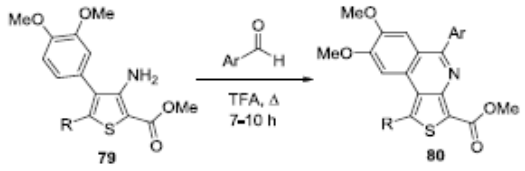


Figure – Bogza synthesis of 3,4-thienoisoquinolines

The previous synthesis employed the use of advanced intermediate heating in trifluoro-acetic acid for an extended period of time. These harsh acidic conditions resulted in low functional group tolerance and would be difficult for large scale applications. As such, a synthesis employing less harsh conditions was envisioned employing palladium catalysis to form multiple bonds in a single step.

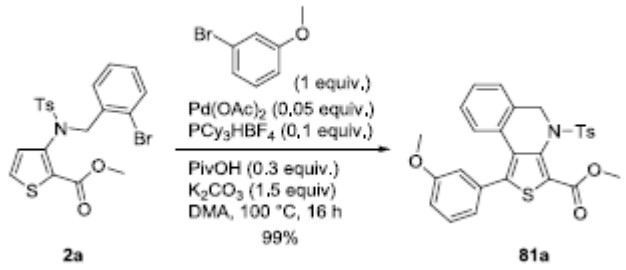


Figure – Double C-H activation reaction towards the synthesis of 3,4-thienoisoquinolines.

In the development of a double C-H activation reaction, initial conditions were derived from the intermolecular C-H activation of heteroaromatics reported by Fagnou and co-worker.49 Subjecting key intermediate, to palladium catalysis conditions with the addition of 3-bromo-anisole was found to give the desired thienoisoquinoline without the requirement for further optimization. The thienoisoquinolines were identified using NMR analysis and further evidence of the synthesis of these compounds by double C-H activation was provided by X-ray crystallography.

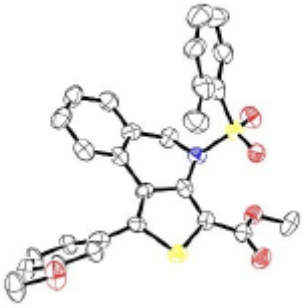


Figure – X-ray structure of a substituted 3,4-thienoisoquinoline

The X-ray structure of a substituted 3,4-thienoisoquinoline clearly portrays the two arylations. An intramolecular C-H activation at C4 generating the unfunctionalized 3,4-thienoisoquinoline and the arylation at C5. Thus, with optimized conditions established and identification of these compounds, the scope of the reaction was explored employing various sulfonamides, aryl bromides and benzyl substituents.

SYNTHESIS OF 2,3-THIENOISOQUINOLINES

Comparable to 3,4-thienoisoquinolines, the 2,3-thienoisoquinoline isomer was hardly reported in the written works however has as of late progressed critical consideration because of its potential as a helpful opposite bosom cancer. Previous blends of the aforementioned combines depended on the combination of the thiophene itself confining the simplicity generally organize broadening. Different blends needed the utilization of combined thiophene two-wheelers confining broadening. One amalgamation concentrating on combining a library of the aforementioned fuses for SAR designs was reported by Wyeth.

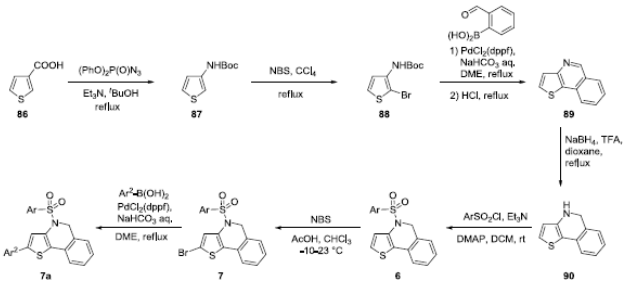


figure – Wyeth synthesis of substituted 2,3-thienoisoquinolines

The Wyeth synthesis begins with industrially ready thiophene-3-carboxylate that experiences a Curtius modification in tBuOH producing the Boc ensured amine. The thiophene is then brominated at C2 specifically utilizing NBS. Brominated thiophene then experiences a Suzuki coupling response accompanied by imine framing and aromatization. Imine was then lessened to the auxiliary amine which was substituted with different sulfonyl-chlorides. Sulfonamide was brominated at C5 to help a second Suzuki response to present different C5-aryl substituents. Granted that this blend takes into account the late stage enhancement at the C5 position, the necessity of a two-stage arylation broadens the length of the amalgamation. Moreover, arylation is confined by the sum of industrially ready boronic harsh corrosive cross-coupling associates. Along these lines, an elective blend was conceived to abbreviate the amount of engineered steps and

increment the potential for enhancement at the C5 position.

From previously synthesized key intermediate, the acid can be unmasked revealing a carboxylic acid. The carboxylic acid can be subjected to decarboxylative cross-coupling conditions to close the centre ring and generate the desired 2,3-thienoisoquinoline system. Using a decarboxylative cross-coupling rather than a C-H activation reaction would allow for selective coupling at the C2 position rather than a potential mixture of isomers derived from arylation at C2 and C4. The C4-H was previously shown to be reactive under C-H activation conditions. The 2,3-thienoisoquinoline can then be functionalized at the C5 position through C-H activation or bromination.

CONCLUSION

In summary, methods have been developed for the synthesis of two isomers of thienoisoquinolines. The syntheses employed the use of modern palladium cross-coupling reactions that are more environmentally friendly compared to their predecessors. These reactions do not require preactivation in the form of organometallic reagents minimizing the quantity of metallic waste produced. Starting from a commercially available thiophene, the key intermediate of both isomers was obtained in 2 steps.

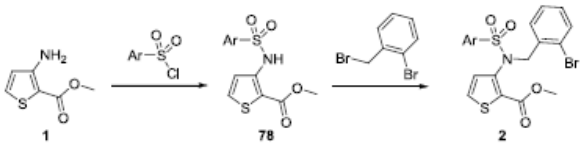


Figure – Synthesis of key intermediate

Synthesis of the key intermediate began with commercially available 3-amino-2-methyl-thiophenecarboxylate and functionalized with a sulfonyl-chloride generating different sulfonamides . Sulfonamides were benzylated using bromobenzylbromide, generating the key intermediate . This two step synthesis was conducted on multigram scale using only recrystalization as a purification method. Recrystalization is a green purification alternative to silica gel chromatography using less solvent and without the requirement of silica gel. The key intermediate was subjected to two different sequences of reactions giving different isomers, which lead to a variety of functionalized thienoisoquinolines.

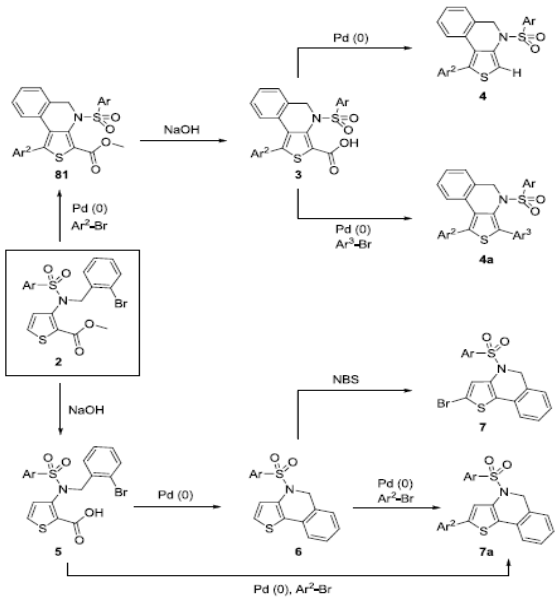


Figure – Summary of the syntheses of functionalized thienoisoquinolines

Subjecting the key intermediate to palladium catalysis conditions with a second aryl bromide facilitates a double C-H activation reaction. An intramolecular C-H activation occurs forming a carbon-carbon bond at generally less reactive C4 position due to an ester functionality at C2 acting as a blocking group. The second C-H activation can occur at the C5 position of the 3,4-thienoisoquinoline functionalizing with a variety of aromatic substituents. The overall process occurred in good to excellent yields for a variety of electronically and sterically different substituents. The ester could be saponified revealing the carboxylic acid giving a synthetic handle for further transformations. The acid can be protodecarboxylated to functionalize the C2 position with a hydrogen that was found to occur readily with a variety of Ar and Ar substituents. The acid could also be subjected under palladium catalysis conditions to undergo a decarboxylative cross-coupling to substitute the C2 position with different aryl substituents. Although the resulting yield was low, further optimization studies are required to increase yield of the transformation.

Altering the order of reactions performed on the key intermediate allowed for the synthesis of functionalized 2,3-thienoisoquinolines . The carboxylic acid was unmasked through a saponification of the corresponding ester. Decarboxylative cross-coupling was then performed on the acid to form unfunctionalized 2,3-thienoisoquinolines. These intermediates were brominated with NBS resulting in functionalization with a bromine at C5. Furthermore, the intermediates, were also functionalized at C5 with a variety of aryl functionalities using C-H activation. The synthesis was further improved by combining both decarboxylative cross-coupling and functionalization through C-H activation into a single

set of conditions. For the one-pot transformation, a palladium/ligand combination, base, reaction temperature and time were optimized. Future work involves the determination of the substrate scope of the transformation.

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