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A One-Pot Double C–H Activation Palladium Catalyzed Route to a Unique Class of Highly Functionalized Thienoisoquinolines

Nicholas W. Y. Wong and Pat Forgione*

Department of Chemistry & Biochemistry, Concordia University, 7141 rue Sherbrooke O. H4B 1R6, Montréal, QC, Canada and Centre for Green Chemistry & Catalysis, Montréal, QC, Canada

pat.forgione@concordia.ca

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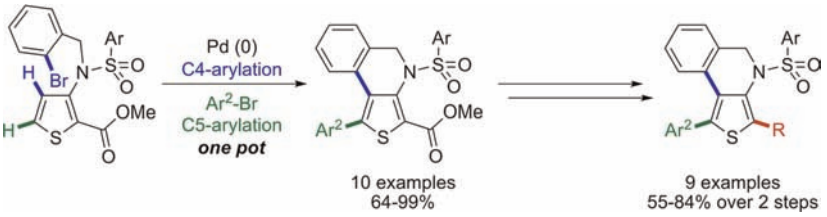
ABSTRACT



The synthesis of a unique class of highly functionalized 3,4-thienoisoquinolines via an efficient palladium-catalyzed one-pot, regioselective double C–H activation is presented. This class of biologically relevant compounds has been prepared in five steps from commercially available starting materials with overall yields ranging from 27 to 62%. A masked carboxylic acid was used to direct C–H activation to the typically less reactive C4 position. Additionally, the carboxylic acid provides a synthetically useful handle for further functionalization.

Heteroaromatics continue to play an important role in the discovery of new drugs against a range of diseases.[1,2] However, a key criterion in drug discovery remains the need to prepare inhibitors that are orally bioavailable. Toward this aim, guidelines have been established to evaluate which lead structures are most likely to achieve this important property.[3] A key criterion is the need to prepare compounds that have a relatively low molecular weight while maintaining high structural diversity. Therefore, the ability to prepare densely functionalized heteroaromatics in a facile and modular manner is important since it allows the exploration of a diverse region of chemical space without significantly increasing the molecular weight of potential lead structures. Toward this end, palladium catalyzed cross-coupling reactions[4] have emerged as an important tool for the preparation of aryl-substituted heteroaromatics in drug discovery.[5] However,

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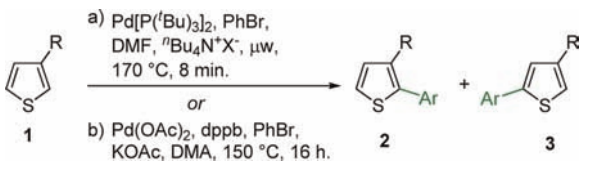
an emerging understanding of the human footprint and the impact on the environment has led to the development of alternatives to classical palladium mediated cross-coupling reactions. C−H activation has emerged as a method to circumvent the requirement of prefunctionalization of the organometallic components.[6,7] Therefore, the ability to perform multiple C−H activation reactions on a substrate using a single set of reaction conditions to prepare densely functionalized heteroaromatics would greatly facilitate library synthesis that is important for drug discovery.

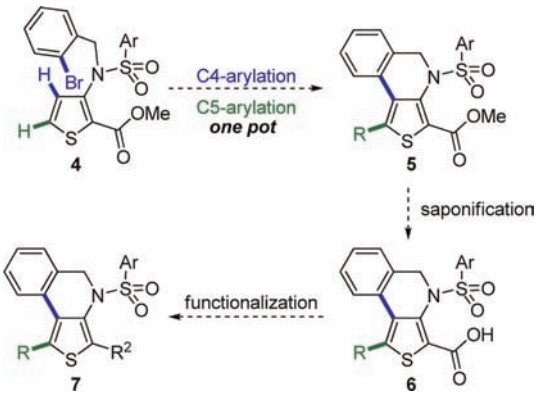
Despite the many advantages of C−H activation, limitations arise when more than one activated hydrogen is available, which leads to selectivity issues. As an example, when 3-methyl thiophene undergoes C−H activation under palladium catalysis conditions (Scheme 1, conditions a) with an aryl-bromide, a mixture of C2-arylation (**2**, R = Me) and C5-arylation (**3**, R = Me) in a 3.3 to 1 ratio is obtained.[8] Doucet provided a solution to this issue by manipulating the C3-susbstituent to favor either C2- or C5-arylation. He demonstrated that employing an aldehyde at the C3-position (**1**, R = CHO) improves the selectivity for C2-arylation (Scheme 1, conditions b, ratio of **2:3** = 81:19, R = CHO). The selectivity could be reversed by increasing the steric bulk at C3 and converting the aldehydes to the corresponding acetal (R = $CH(OEt_2)$ to obtain C5−H activation as the major product (ratio of **3:2** = 24:76, R = $CH(OEt)_2$) (Scheme 1, conditions b).[9] Although an improvement in selectivity was achieved, a mixture of products was obtained in all cases and isolated yields of the desired isomer were modest.

Scheme 1. C2- vs C5-Arylation



During our efforts to prepare thienoisoquinoline inhibitors of estrogen receptor NFκB,[10] we proposed a double arylation (Scheme 2) of an advanced intermediate (**4**) to streamline the synthesis of these densely functionalized heteroaromatics. To prepare these highly functionalized thienoisoquinolines and circumvent the limitation of C−H activation selectivity, we envisioned employing a carboxylic acid derivative at the C2-position that allows for a single set of conditions to undertake both C4-intramolecular arylation and C5-intermolecular arylation simultaneously. The masked carboxylic acid group would direct intramolecular C4−H activation while also allowing exclusive intermolecular arylation at C5. The Itami group has demonstrated elegant conditions to selectively arylate the C4-position of thiophenes;[11] however our route required conditions that would allow both C4 and C5 arylation to occur simultaneously. The carboxylic acid could then be unmasked providing a synthetic handle for further functionalization.[8,12,13] To our knowledge, only one synthesis of these biologically important compounds has been reported by the group of Bogza, which required the heating of an advanced intermediate under harsh acidic conditions at elevated temperatures for an extended period of time.[14]

Scheme 2. Proposed Route towards Thienoisoquinolines



Our modular synthesis begins with a commercially available thiophene (**8**) which was functionalized with a variety of sulfonyl chlorides resulting in the corresponding sulfonamides. These sulfonamides were subsequently benzylated in good to excellent yields over two steps giving rise to the functionalized key intermediates (**4**) (Table 1).

Benzyl-sulfonamides (**4a**−**g**) were then subjected to double C−H activation conditions with a variety of aryl-bromides (Table 2). Rewardingly, this double

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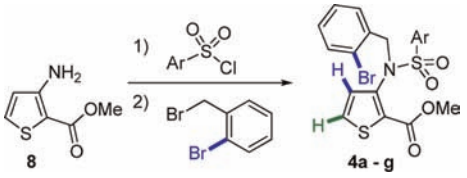
Table 1. Synthesis of Key Intermediate

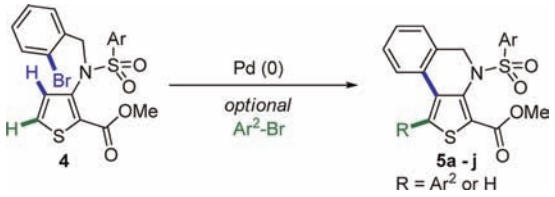


entry	Ar	product	yield[a] (%)
1	4-Me-C_6H_4	**4a**	76
2	3-Me-C_6H_4	**4b**	69
3	2-Me-C_6H_4	**4c**	87
4	4-MeO-C_6H_4	**4d**	79
5	4-O_2N-C_6H_4	**4e**	41
6	4-F-C_6H_4	**4f**	61
7	2-thiophene	**4g**	63

[a] Yields over two steps, isolated and characterized after each step. (1) Aryl sulfonyl chloride (1.5 equiv) was added to a solution of **8** (1 equiv) in pyridine (0.8 M) and was heated to 50 °C for 1 h. (2) Bromobenzyl-bromide (1.2 equiv) was added to a solution of K_2CO_3 (2 equiv), and sulfonamide (1 equiv) in DMF (0.3 M) and heated to 50 °C for 16 h.

C4/C5-arylation protocol yielded a wide range of desired products in high yields. Although coupling with bromobenzene (entry 1) proceeded in modest yield, all other couplings proceeded in very good to excellent yields, including both electron rich (entries 2, 3, and 6–9) and electron poor (entries 4, 5) aryl-bromides. Importantly, the efficiency of the reaction is demonstrated by only requiring 1 equiv of aryl-bromide. Lastly, without the addition of an external aryl-bromide, C4-arylation is obtained exclusively in excellent yield (entry 10).

Table 2. Double C–H Activation Scope[a]



entry	Ar	R	product	yield (%)
1	4-Me-C_6H_4	C_6H_5	**5a**	64
2	4-Me-C_6H_4	3-MeO-C_6H_4	**5b**	99
3	4-Me-C_6H_4	4-MeO-C_6H_4	**5c**	90
4	4-Me-C_6H_4	3-EtOOC-C_6H_4	**5d**	97
5	4-Me-C_6H_4	4-EtOOC-C_6H_4	**5e**	81
6	3-Me-C_6H_4	3-MeO-C_6H_4	**5f**	80
7	2-Me-C_6H_4	3-MeO-C_6H_4	**5g**	81
8	4-MeO-C_6H_4	3-MeO-C_6H_4	**5h**	79
9	4-F-C_6H_4	3-MeO-C_6H_4	**5i**	90
10	4-Me-C_6H_4	H	**5j**	96

[a] Ar^2–Br (1 equiv) was added to a solution of **4** (1 equiv), $Pd(OAc)_2$ (0.05 equiv), $PCy_3 \cdot HBF_4$ (0.1 equiv), PivOH (0.3 equiv), K_2CO_3 (1.5 equiv) in DMF (0.1 M) and heated to 100 °C for 6 h.

Preparation of our model substrate (Table 2, entry 2) demonstrates the potential of this sequence on an industrial scale. The three-step, four-reaction process was performed on a gram scale converting **8** to **5b** in a 75% overall yield using only recrystallization and trituration as purification techniques, circumventing the need for large quantities of silica gel for purification.

The methyl ester present at C2 was employed to direct the intramolecular arylation at C4 and allow C5-intermolecular arylation to occur exclusively and in high yields. Subsequently, the ester was hydrolyzed in quantitative yields and the resulting acid was subjected to proto-decarboxylation (Table 3). The corresponding product was obtained over two steps in yields ranging from moderate to excellent and tolerates a variety of substituents. The products **7a**–**i** can be further arylated at C2 via C–H activation.

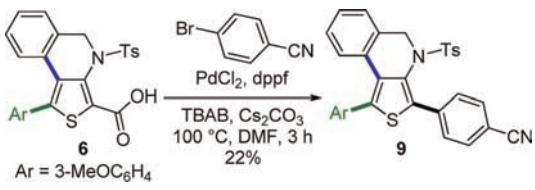
Table 3. Proto-decarboxylation[a]

entry	Ar	Ar^2	product	yield (%)
1	4-Me-C_6H_4	C_6H_5	**7a**	55
2	4-Me-C_6H_4	3-MeO-C_6H_4	**7b**	65
3	4-Me-C_6H_4	4-MeO-C_6H_4	**7c**	78
4	4-Me-C_6H_4	3-HOOC-C_6H_4	**7d**	84
5	4-Me-C_6H_4	4-HOOC-C_6H_4	**7e**	70
6	3-Me-C_6H_4	3-MeO-C_6H_4	**7f**	69
7	2-Me-C_6H_4	3-MeO-C_6H_4	**7g**	70
8	4-MeO-C_6H_4	3-MeO-C_6H_4	**7h**	68
9	4-F-C_6H_4	3-MeO-C_6H_4	**7i**	78

[a] **5** was dissolved in a 1:2:1 mixture of 2 M NaOH/THF/MeOH and brought to reflux for 1 h. The resulting acid (**6**) was isolated and then dissolved in DMF. **6** in DMF was then added to a microwave vial containing $PdCl_2$ (0.05 equiv), $P^tBu_3 \cdot HBF_4$ (0.05 equiv), and Cs_2CO_3 (1.5 equiv) purged with argon, sealed, and irradiated at 170 °C for 8 min.

Additionally, preliminary results demonstrate that the carboxylic acid can be used as a synthetic handle for direct arylation via decarboxylative cross-coupling (Scheme 3); current efforts are focused on optimizing this transformation.

Scheme 3. Decarboxylative Cross-Coupling



In conclusion, we have reported an efficient, modular synthesis of highly substituted 3,4-thienoisoquinoline systems, featuring a one step palladium-catalyzed regioselective double C−H activation, from a commercially available thiophene. The use of a masked carboxylic acid promotes intramolecular C4-arylation and intermolecular C5-arylation in a single pot in excellent yields. This method provides facile access to a densely functionalized biologically important set of heteroaromatics. Current research is aimed toward the further functionalization of the thiophene core employing the carboxylic acid as a synthetic handle.

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

The authors declare no competing financial interest.