Organic LETTERS

Letter

pubs.acs.org/OrgLett

Mild and Efficient One-Pot Synthesis of 2-(Perfluoroalkyl)indoles by Means of Sequential Michael-Type Addition and Pd(II)-Catalyzed Cross-Dehydrogenative Coupling (CDC) Reaction

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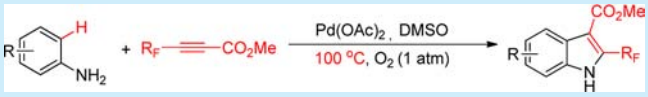
Supporting Information

ABSTRACT: 2-Perfluoroalkylated indoles were efficiently synthesized via a one-pot cascade Michael-type addition/palladium-catalyzed intramolecular cross-dehydrogenative coupling (CDC) process, using molecular oxygen as the sole oxidant at 100 °C in DMSO. This process allows atom economical assembly of indole rings from inexpensive and readily available anilines and methyl perfluoroalk-2-ynoates and tolerates a broad range of functional groups.



The indole subunit is ubiquitous in naturally occurring compounds as well as designer therapeutic agents.[1,2] Numerous methods have thus been developed for its synthesis.[3] In recent years, transition-metal catalyzed cross-coupling via C−H activation has received increased attention as an alternative strategy for indole synthesis due to its improved atom and step economy.[3h]

In this context, direct oxidative intramolecular cross-dehydrogenative coupling (CDC) of commercially available anilines and alkynes is of particular interest.[4] However, the majority of the current methods heavily involved the use of stoichiometric oxidants, such as $Cu(OAc)_2$, AgOAc, $PhI(OAc)_2$, and TBHP, to maintain the catalytic cycle.[5] Therefore, the outcome of these procedures produces large amounts of waste. To solve this problem, it is attractive to use O_2 as the oxidant so that only water was produced in the reaction process.[6] In 2009, a Pd(II)-catalyzed process with O_2 as the sole oxidant for synthesis of indoles was reported by Jiao and co-workers.[4d] The reactions of anilines and symmetrical electron-deficient alkynes (dialkyl acetylenedicarboxylate) with Jiao's catalytic system proceeded efficiently at 120 °C in DMA.

Keeping the knowledge of their work in mind, we reasonably envisioned that Jiao's catalytic system might be utilized for direct 2-perfluoroalkylated indole synthesis. Thus, in continuation of our interest in the synthesis of biologically active perfluoroalkylated heterocycles,[7] herein, we report a one-pot sequential Michael-type addition/Pd(II)-mediated intramolecular C−H/C−H CDC reaction of anilines and unsymmetrical electron-deficient alkynes (methyl perfluoroalk-2-ynoates) under milder conditions than Jiao's work.

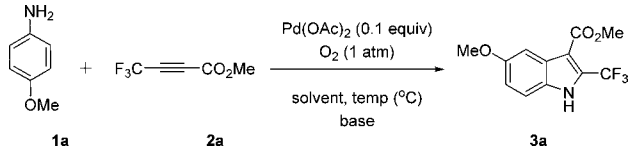
We initiated our study by examining the cyclization of 4-methoxyaniline **1a** with methyl 4,4,4-trifluoro-but-2-ynoate **2a**. Under Jiao's conditions (10 mol % $Pd(OAc)_2$/DMA−PivOH (4:1 v/v)/ O_2/120 °C) within 12 h, the desired product methyl 5-methoxy-2-(trifluoromethyl)-1*H*-indole-3-carboxylate **3a** was isolated in 75% yield (Table 1, entry 1). A similar yield was obtained when the reaction was conducted at 100 °C (Table 1, entry 2). However, a lower temperature (80 °C) deteriorated the product yield (Table 1, entry 3). Clear improvement of the yield was observed when $NaHCO_3$ (0.1 equiv) was added, and a mixture of DMSO and PivOH (4:1) acted as the most suitable reaction medium, enhancing the yield of **3a** to 89% (Table 1, entry 6). Other bases did not show apparent positive effects (Table 1, entries 9−13). Addition of 0.05, 0.2, and 0.3 equiv of $NaHCO_3$ led to generation of the product in 77%, 80%, and 75% yields respectively (Table 1, entries 14−16). It was also found that employing an air atmosphere dramatically lessened the yield of **3a** just as reported by Jiao and co-workers. Therefore, the best reaction conditions were concluded as follows: anilines **1**, alkynes **2**, $Pd(OAc)_2$ (catalyst), $NaHCO_3$ (base), and O_2 in DMSO−PivOH 4:1 (v/v, solvent) at 100 °C.

The limitations were assessed with different anilines and three perfluoroalkylated internal alkynes (Scheme 1). All monosubstituted, disubstituted, or fused anilines, including

Received: May 20, 2015
Published: June 19, 2015

DOI: 10.1021/acs.orglett.5b01479
Org. Lett. 2015, 17, 3283−3285

Table 1. Modification of Jiao's Reaction Conditions[a]

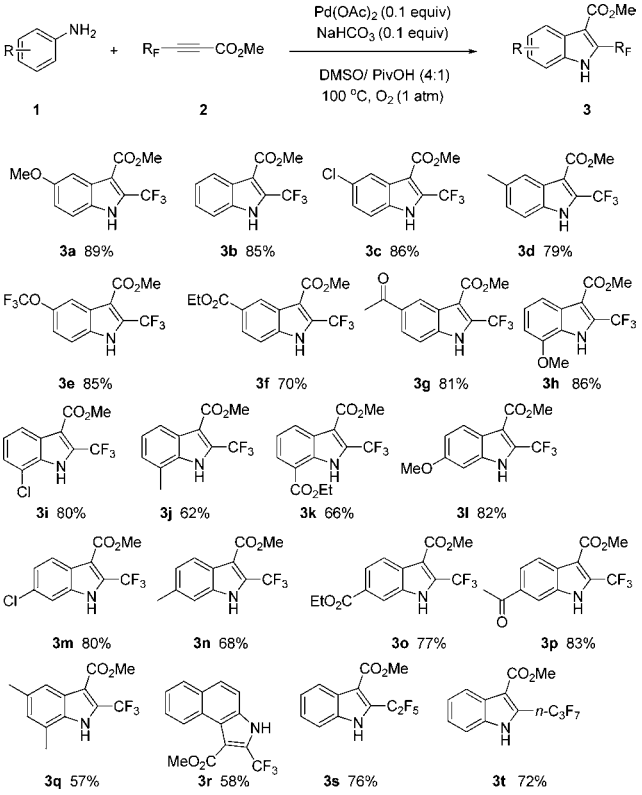


1a 2a 3a

entry	solvent[b]	base (equiv)	temp (°C)	yield (%)[c]
1	DMA/PivOH	$NaHCO_3$ (0)	120	75
2	DMA/PivOH	$NaHCO_3$ (0)	100	72
3	DMA/PivOH	$NaHCO_3$ (0)	80	55
4	DMA/PivOH	$NaHCO_3$ (0.1)	100	80
5	DMF/PivOH	$NaHCO_3$ (0.1)	100	60
6	DMSO/PivOH	$NaHCO_3$ (0.1)	100	89
7	toluene/PivOH	$NaHCO_3$ (0.1)	100	63
8	1,4-dioxane/PivOH	$NaHCO_3$ (0.1)	100	25
9	DMSO/PivOH	NaOH (0.1)	100	65
10	DMSO/PivOH	Na_2CO_3 (0.1)	100	80
11	DMSO/PivOH	K_3PO_4 (0.1)	100	71
12	DMSO/PivOH	DIPEA (0.1)	100	61
13	DMSO/PivOH	Et_3N (0.1)	100	53
14	DMSO/PivOH	$NaHCO_3$ (0.05)	100	77
15	DMSO/PivOH	$NaHCO_3$ (0.2)	100	80
16	DMSO/PivOH	$NaHCO_3$ (0.3)	100	75

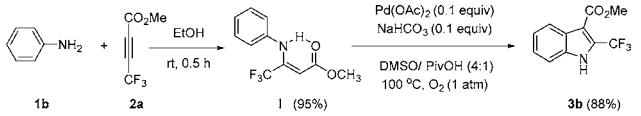
[a]General conditions: **1a** (1.0 mmol), **2a** (1.2 equiv), $Pd(OAc)_2$ (0.1 equiv), base, solvent/PivOH 4:1 v/v (5.0 mL), O_2 (1 atm), 12 h. [b]All the solvents were dried and distilled before use. [c]Isolated yield.

Scheme 1. Direct 2-Perfluoroalkylated Indole Synthesis under the Modified Jiao Reaction Conditions[a,b]

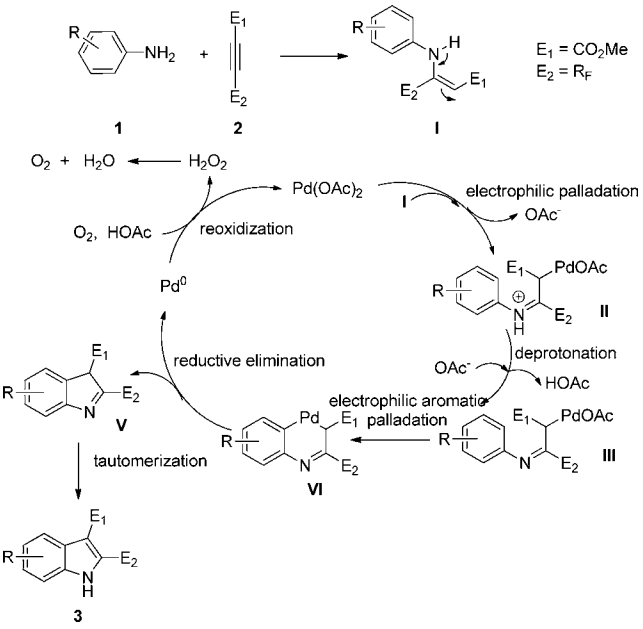


[a]General conditions: aniline **1** (1.0 mmol), methyl perfluoroalk-2-ynoate **2** (1.2 mmol), $Pd(OAc)_2$ (0.1 equiv), $NaHCO_3$ (0.1 equiv), O_2 (1 atm), DMSO/PivOH (4:1 v/v, 5 mL), 100 °C, 12 h. [b]Isolated yield.

Scheme 2. Stepwise Michael Addition and Intramolecular Cross-Dehydrogenative Coupling



Scheme 3. Proposed Catalytic Cycle of the Palladium(II)-Catalyzed Indole Formation through CDC



ortho-substituted substrates, underwent the reaction smoothly and afforded the corresponding products in moderate to good yields. For the *para*-substituted anilines, both electron-withdrawing and -donating groups, such as −OMe, −Cl, −Me, $-OCF_3$, $-CO_2Et$, and −COMe, were tolerant under the reaction conditions (Scheme 1, **3a**, **3c**−**g**). For *meta*-substituted anilines, the less hindered position was alkylated with excellent selectivities and gave varying yields ranging between 68% and 83% (Scheme 1, **3l**−**p**). Anilines with strong electron-withdrawing groups such as $-NO_2$ afforded no product at all. The ring-fused 2-naphthalenamine also participated in this reaction and afforded product **3r** in 58% yield (Scheme 1). A slightly lower yield was obtained for indole derivative **3s** or **3t**, likely due to the steric hindrance of the long-chain perfluoroalkyl group.

To probe the reaction mechanism, the Michael-type adduct of **1b** and **2a**, (*E*)-methyl 4,4,4-trifluoro-3-(phenylamino)but-2-enoate **I**, was isolated and tested under the standard reaction conditions, affording **3b** in 88% yield (Scheme 2), which indicates that enamine **I** could be a potential intermediate in the transformation.

On the basis of the previous mechanistic studies[3c,4c,d,8] and the above experimental results, a Pd^{II}/Pd^0 redox process was proposed: the transformation begins with an electrophilic palladation of the nucleophilic enamine **I**, which is generated by Michael-type addition of aniline and alkyne, followed by deprotonation. The resulting palladium complex **III** is suitable for electrophilic aromatic palladation by a concerted metalation−deprotonation (CMD) mechanism. Subsequent reductive elimination generates the 3*H*-indole product **V** which can tautomerize quickly to give the indole product **3** and a Pd^0

DOI: 10.1021/acs.orglett.5b01479
Org. Lett. 2015, 17, 3283−3285

complex, which is reoxidized by O_2 in the presence of acid to regenerate the active catalyst for the next catalytic cycle (Scheme 3). The role of $NaHCO_3$ in this reaction is unclear and might help to adjust the acidity of the reaction system.

In summary, we have developed a mild and efficient one-pot method to prepare 2-perfluoroalkylated indoles. The sequential Michael type-addition/Pd(II)-catalyzed CDC reaction of anilines with alkynes only required O_2 as an external oxidant. And it was highly regioselective when unsymmetrical internal alkynes such as methyl perfluoroalk-2-ynoates were employed. Considering the valuable structure of the products and good functionality tolerance, this reaction should be of synthetic utility.

■ ASSOCIATED CONTENT

Supporting Information

General information, optimization of the reaction condition, copies of ^1H NMR, ^{13}C NMR, and ^{19}F NMR spectra for all compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01479.

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Author Contributions

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors greatly acknowledge the National Natural Science Foundation of China (Grant No. 21272152) and Yang Fan Program of Shanghai Municipal Science and Technology Commission (Grant No. 15YF1404200).

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Org. Lett. 2015, 17, 3283−3285