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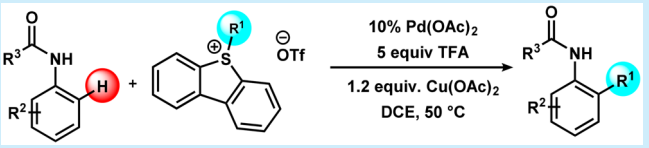
Sulfonium Salts as Alkylating Agents for Palladium-Catalyzed Direct Ortho Alkylation of Anilides and Aromatic Ureas

Dániel Cs. Simkó, Péter Elekes, Vivien Pázmándi, and Zoltán Novák*

ELTE "Lendület" Catalysis and Organic Synthesis Research Group, Department of Organic Chemistry, Faculty of Science, Eötvös University, Pázmány P. stny. 1/A, H-1117 Budapest, Hungary

Supporting Information

ABSTRACT: A novel method for the *ortho* alkylation of acetanilide and aromatic urea derivatives via C−H activation was developed. Alkyl dibenzothiophenium salts are considered to be new reagents for the palladium-catalyzed C−H activation reaction, which enables the transfer of methyl and other alkyl groups from the sulfonium salt to the aniline derivatives under mild catalytic conditions.

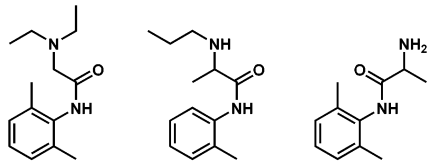


C−C bond-forming reactions via aromatic C−H bond-activation processes have been intensively studied during recent decades.[1] Although several methods are described to evaluate $C(sp^2)-C(sp^2)$ couplings on aromatic substrates, C−H activation based direct alkylations by alkyl group transfer are less explored in the field.[2] However, the presence of alkyl groups, especially the ubiquitous methyl group in molecular scaffolds, could have beneficial effects on biological properties.[3] For this reason, the expansion of available alkylation methodologies is an important task for organic syntheses with special regard to late-stage functionalization approaches.

Amide functional groups are excellent moieties in guided C−H activation to functionalize aromatic C−H bonds. Taking advantage of the beneficial properties of this directing group, palladium-catalyzed *ortho* functionalization of acetanilide derivatives under mild reaction conditions has been widely studied.[4] Supported by the use of arylboronic acids[5b,c] and iodides,[5d,e] these methods enable the introduction of aryl groups into substrates. Alkenylation reactions have been studied in detail and developed by Leeuwen, Youn, and Hii among other research groups.[6] Although one of the earliest examples of C−H activation reactions described the direct alkylation of anilides using stoichiometric palladium,[7] the introduction of alkyl groups under catalytic conditions has remained a challenging task, especially under mild reaction conditions.[8] Existing alkylation methods often suffer from the loss of selectivity or byproduct formation, as chain isomerization in Friedel−Crafts or β-H-elimination in transition-metal-catalyzed coupling reactions. Additionally, to the best of our knowledge there is only one existing method for the *ortho* alkylation of aromatic ureas through direct C−H bond functionalization, considering both traditional and transition-metal-catalyzed methods.[9]

Aside from the utilization of acetanilides in academic research as suitable substrates for transition-metal-catalyzed C−H bond functionalizations, the aniline derivatives bearing a methyl group in the *ortho* position, such as lidocaine, prilocaine, and tocainide, have significant biological activities and medicinal applications as local anesthetics (Scheme 1).

Scheme 1. Biologically Active *o*-Methylanilide Derivatives



Electrophilic reagents, such as iodonium salts, are efficient coupling partners in C−H activation reactions.[10] We previously have demonstrated that a novel fluoroalkyl iodonium salt is an excellent alkyl source for C−H bond functionalization to alkylate indoles[11] and aniline derivatives.[9,12] In our research program, we focused on the expansion of the alkylations via C−H activation, which can be performed under mild conditions. To achieve this, we intended to use electrophilic alkyl sources, which could have high reactivity for mild functionalizations. Unfortunately, alkyliodonium salts are not stable enough to this purpose; therefore, the design of novel alternative reagents was necessary. Considering the properties of onium salts, alkylsulfonium salts could provide an alternative solution. However, only trifluoromethylations have been developed yet with these type of onium reagents by Yu[13] and Shi[14] using Umemoto's reagent[15] for the *ortho* functionalization of aromatic amide and phenylpyridine derivatives.

For the synthesis of the sulfonium salts, we used two approaches (Scheme 2). The alkylation of dibenzothiophene can be performed with formate esters in strong acidic media[16] or with alkyl iodide in the presence of silver tetrafluoroborate.[17] Weakly coordinating anions are important in C−H activation,

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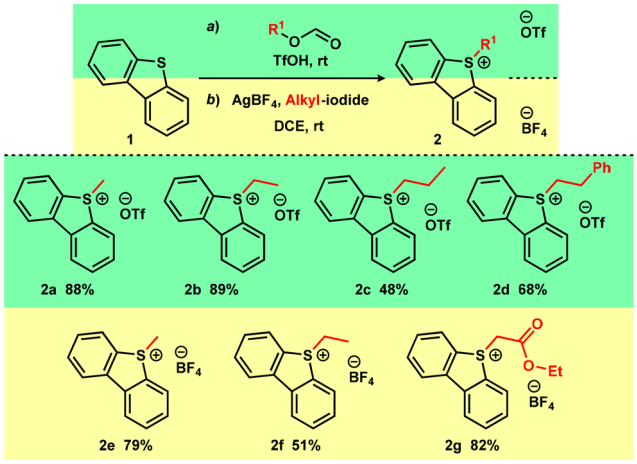
Scheme 2. Synthesis of Alkylsulfonium Salts with Formate Esters or Silver Tetrafluoroborate[a]

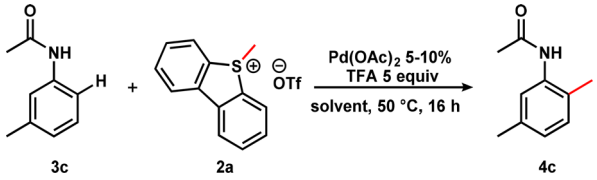


[a]Reaction conditions: (a) 1 equiv of **1**, 2 equiv of formate ester, 6 equiv of triflic acid; (b) 1 equiv of **1**, 1 equiv of $AgBF_4$, 3–6 equiv of alkyl iodide in dichloroethane. Isolated yields.

therefore we prepared the salts with BF_4 and triflate counterions. In comparison, the acid induced method, using esters, is cheaper and seemed to be more robust, hence we used it for gram-scale preparation of the salts (2–50 mmol scales).

Parallel to the synthesis of alkylsulfonium salts, we optimized the reaction parameters necessary for the efficient *ortho* methylation of anilides. On the basis of our earlier studies on the C–H activation of anilide derivatives, we chose palladium acetate as catalyst and trifluoroacetic acid as additive for the initial studies. First, we compared the conversions of the reaction of 3′-methylacetanilide and *S*-methyldibenzothiophenium triflate in different solvents. We found that in polar solvents the reaction did not work, but less polar, nonprotic solvents such as toluene, DCM, and DCE were suitable for the transformation (Table 1, entries 1–7). Regarding the catalyst loading, the conversion of the reaction changed proportionally

Table 1. Optimization Studies[a]



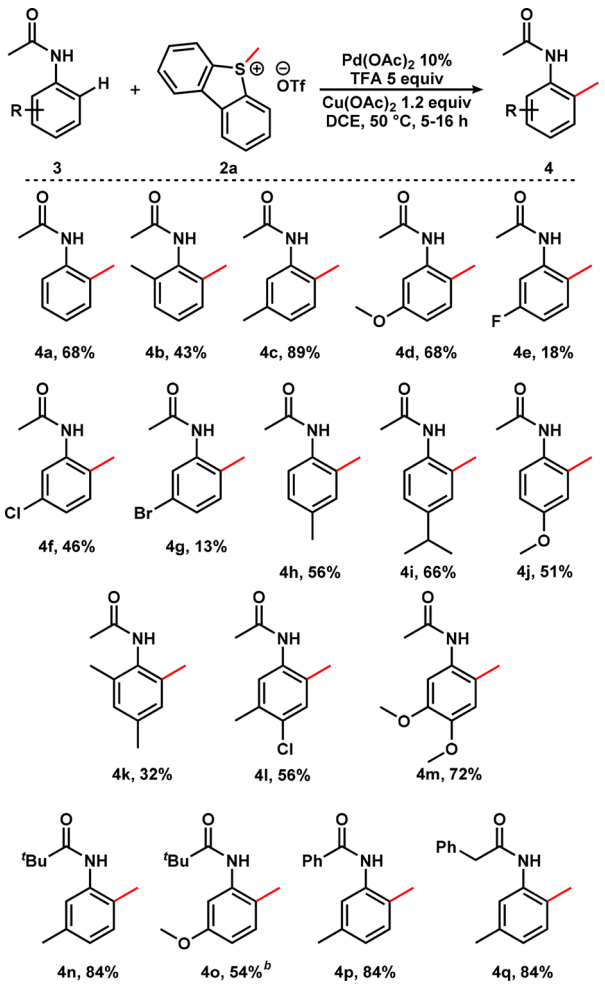
entry	$Pd(OAc)_2$ (mol %)	solvent	GC yield (%)
1	7.5	MeOH	0
2	7.5	MeCN	0
3	7.5	acetone	0
4	7.5	EtOAc	53
5	7.5	toluene	79
6	7.5	DCM	76
7	7.5	DCE	81
8	5	DCE	70
9	10	DCE	86
10	7.5	DCE	98[b]

[a]Reaction conditions: 1 equiv of **3** (0.05 mmol), 1.2 equiv of **2**, $Pd(OAc)_2$ 5–10 mol %, TFA 5 equiv, solvent 0.5 mL. Yields determined by GC analysis. [b]1.2 equiv of $Cu(OAc)_2$ was used as additive

to the amount of palladium (entries 8 and 9). Additionally, the presence of 5 equiv acid was found to be necessary for the complete suppression of the formation of *N*-alkylated by-product. As a further development of the coupling we probed the effect of copper acetate because of its general use as an additive for palladium catalyzed C–H activation.[18] To our delight, a significant increase of the conversion was observed (98%, Table 1, entry 10).[19]

Under the optimized reaction conditions, we explored the substrate scope of the alkylation. First, acetanilide derivatives were methylated with *S*-methyldibenzothiophenium salt (Scheme 3). The simple 2′-methylacetanilide (**4a**) was isolated

Scheme 3. Methylation of Acetanilide Derivatives[a]



[a]Reaction conditions: 1 equiv of **3** (1 mmol), 1.2 equiv of **2**, $Pd(OAc)_2$ 10 mol %, TFA 5 equiv, $Cu(OAc)_2 \cdot H_2O$ 1.2 equiv, in 10 mL of DCE at 50 °C. Isolated yields. [b]Conversion, based on NMR measurement; product was isolated as a mixture of the SM and **4o** (ratio SM: **4o** is 46:54).

in 68% yield. Substituents at the *ortho*, *meta* and *para* positions are tolerated, and the appropriate products **4b–j** were isolated in 13–89% yield range. Although the methylation took place more efficiently in the presence of electron donating functional groups, the F and Br substituted aromatic products (**4e** and **4g**) were obtained only in poor yields. Similarly to the monosubstituted substrates, electron rich anilines equipped with two substituents on the aryl ring were *ortho* methylated and products **4k–m** were prepared in 32–72% yield. As a

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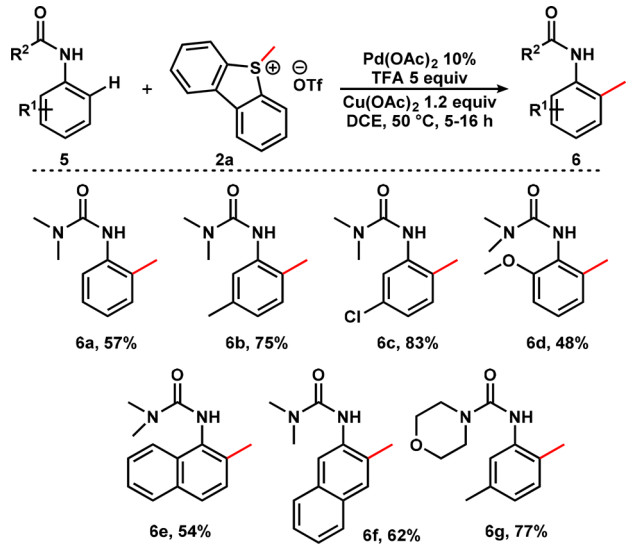
general reactivity pattern, electron rich rings favor the coupling, but the presence of electron donating groups in the *para* position to the amide directing group can lead the formation of dimethylated side products. Therefore, these reactions gave moderate yields of products **4h−j** after separation and purification. As a limitation, the presence of electron-withdrawing groups (acetyl, nitro) on the aromatic ring did not allow for functionalization. Polar functional groups (amine, free OH) on the acetyl directing moiety were not tolerated as well (not shown). At the same time, sterically hindered anilides can be transformed easily. Bulky groups on the directing amide group had no deleterious effect on the methylation and products **4n−q** were isolated in good 75−84% yield.

Beside anilide derivatives, we aimed to explore the *ortho* methylation of aromatic ureas for the first time. We found that *N,N*-dimethylamino and morpholino urea functions behave as excellent directing groups for the palladium-catalyzed C−H activation. The alkylations with the methyldibenzothiophenium salt took place with similar efficiency to the anilides (Scheme 4)

Scheme 4. Methylation of Aromatic Ureas[a]



[a]Reaction conditions: 1 equiv of **3** (1 mmol), 1.2 equiv of **2**, $Pd(OAc)_2$ 10 mol %, TFA 5 equiv, $Cu(OAc)_2{\cdot}H_2O$ 1.2 equiv, in 10 mL of DCE at 50 °C. Isolated yields.

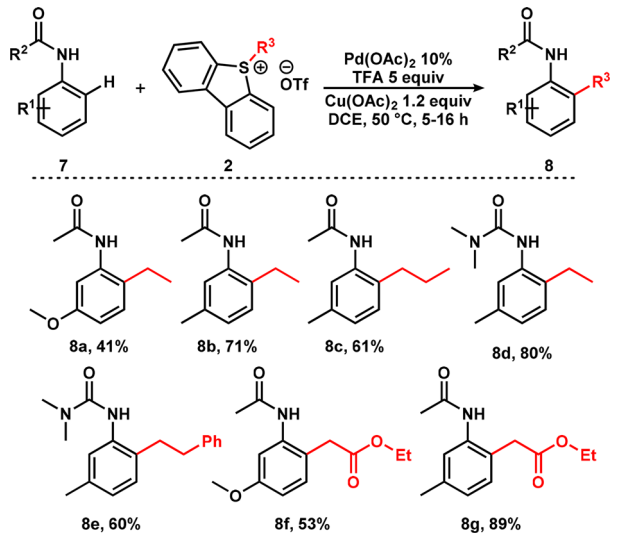
under optimized catalytic conditions. Substituted phenylureas and naphthylureas were successfully methylated in the *ortho* position leading to products **6a−g**, which were isolated in 48−83% yield.

Finally, we studied the extension of the alkylation method beyond methyl group transfer. Reactions were carried out under the optimized conditions with the previously prepared *S*-alkylsulfonium salts. We found that the *ortho* alkylation of anilides and aromatic ureas can be achieved under mild reaction conditions (Scheme 5).

Ethyl, propyl, phenethyl and carboxymethylene groups were introduced onto the *ortho* position to the directing group. 2′-Alkylacetanilides **8a−c,f,g** were isolated in 41−89% yield, while 2′-alkylurea derivatives **8d,e** were obtained in 60−80% yield, respectively.

To increase the efficiency of the procedure, dibenzothiophene, the precursor of the alkylating agents, was recovered by isolation from the reaction mixture of **4c,k** and **6a,d**, and

Scheme 5. Different Alkyl Groups[a]



[a]Reaction conditions: 1 equiv of **3** (1 mmol), 1.2 equiv of **2**, $Pd(OAc)_2$ 10 mol %, TFA 5 equiv, $Cu(OAc)_2{\cdot}H_2O$ 1.2 equiv, in 10 mL of DCE at 50 °C. Isolated yields.

dibenzothiophene was recovered in a range of 70−99% efficiency.

In summary, we have developed a new and efficient catalytic method for the direct alkylation of aromatic amide and urea derivatives with the utilization of palladium catalyzed C−H activation under mild reaction conditions. We demonstrated that *S*-alkyldibenzothiophenium salts are suitable alkylating reagents for the C−H activation. Additionally, with the aid of this reagent the alkylation of aromatic ureas can be achieved for the first time. The prepared sulfonium salts are considered to be new reagents in such transformations, and hence, hopefully their applicability could open new reaction paths in the field of transition-metal-catalyzed C−H activation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03813.

Processes, experimental details, and spectral data for products (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: novakz@elte.hu.

ORCID

Zoltán Novák: 0000-0001-5525-3070

Notes

The authors declare no competing financial interest.

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(18) For such reaction conditions, see refs 13 and 14.

(19) For further information, see the Supporting Information

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