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A one-pot process for palladium catalyzed direct C–H acylation of anilines in water using a removable *ortho* directing group†

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A new mild, practical method for the synthesis of aminobenzophenone derivatives through a three step one-pot reaction sequence involving acylation of anilines, palladium catalyzed cross-dehydrogenative coupling of the formed anilides and the hydrolytic cleavage is reported. The full reaction sequence was performed under aqueous conditions.

Oxidative C–H bond activation is one of the most important topics in recent synthetic organic chemistry.[1] Compared to cross coupling reactions, the preactivation of the substrate is not needed for the introduction of new functional groups and the formation of by-products can be reduced. Using oxidative C–H couplings, a wide range of biaryl structures can be synthesized[2] that can potentially be the building blocks of biologically active natural products.[3] A key challenge in C–H activation chemistry is controlling the regioselectivity. The presence of a directing group in arenes ensures selective activation of C–H bond through interaction with the transition metal catalyst during the reaction.[4]

Although, the large part of the C–H activation reactions takes place in organic media, there are several examples for reactions which are conducted in more environmentally benign solvent such as water.[5]

In the past few years, several synthetic methodologies were developed for the synthesis of benzophenone derivatives *via* palladium catalyzed *ortho* selective cross dehydrogenative C–H coupling. For these transformations O-phenylcarbamates, 2-arylpiridines, and mostly acetanilides are the substrates, which can be acylated with aldehydes,[6] carboxylic acids,[7] ketocarboxylic acids[8] or toluene[9] derivatives. In these homogenous organic reactions $Pd(TFA)_2$ or $Pd(OAc)_2$/TFA was the most effective catalyst, and TBHP as oxidant provided the best yields.

Recently, our group reported a mild implementation of this palladium-catalyzed coupling in aqueous media.[10] We performed the reaction in water at RT in the presence of catalytic amount of SDS (sodium dodecylsulfate). The surfactant additive highly accelerates the reaction.[11] Taking advantage of these conditions we synthesized several *N*-(2-benzoylphenyl) acetamide derivatives from *N*-phenylacetamides.

N-Phenylacetamide substrates can be prepared from anilines with acetic anhydride in organic solvents.[12] However, Patel *et al.* showed that the protection of anilines took place straightforwardly under aqueous conditions with the support of SDS at room temperature.[13] Based on this aqueous *N*-acylation procedure and our previously developed palladium catalyzed coupling, we supposed that the aniline protection step and the C–H acylation step can be carried out successively in one pot using SDS/water as a solvent. This strategy would enable the one-pot *ortho* acylation of anilines *via* protection-coupling sequence under aqueous conditions, and also offers the possibility for the final deprotection of the anilides after the coupling to provide aminobenzophenones. In this three step synthesis, the acetyl group serves as a removable *ortho* directing group for C–H activation.

To demonstrate the compatibility of the procedures for aniline protection and the palladium-catalyzed *ortho* acylation, we treated aniline (**1a**) with 1.5 equivalents of acetic anhydride in SDS/water at room temperature. The acylation took place with full conversion after 0.5 hours providing the acetanilide as suitable substrate for C–H activation. Then we added 5 mol% $Pd(OAc)_2$ catalyst, 26 mol% TFA, 2 eq. benzaldehyde (**3a**) and 2 eq. TBHP (Scheme 1) as the most efficient oxidant in this coupling.

To our delight, at room temperature we observed the transformation of acetanilide (**2a**) to *N*-(2-benzoylphenyl)acetamide (**4a**) with 77% conversion after 4 hours, and complete reaction after 24 hours. This reaction sequence demonstrated the

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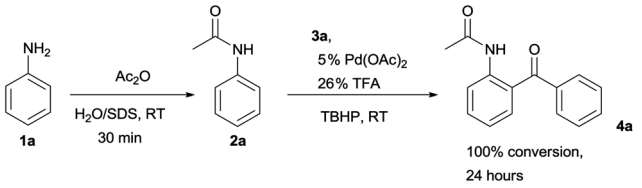
† Electronic supplementary information (ESI) available: Results of the optimization studies, experimental procedures and the characterization data for the products are available. The identity and purity of the known products was confirmed by ^1H and ^{13}C NMR spectroscopic analysis, and the new products were fully characterized. See DOI: 10.1039/c3ra45160g

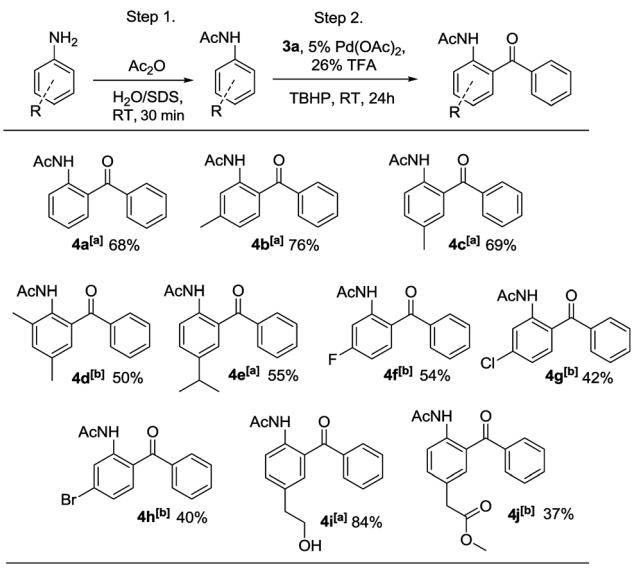


Scheme 1 One-pot *ortho* acylation of anilines *via* N protection and *ortho* C–H activation.

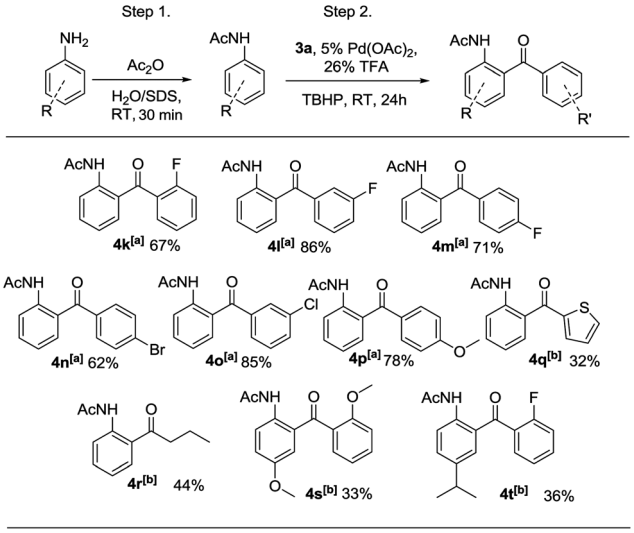
compatibility of the N and C acylation, therefore we aimed to explore the substrate scope of this reaction sequence for the preparation of acetamido benzophenones. It is of note that the acetic acid formed from anhydride during the acylation and hydrolysis does not disturb the following palladium catalyzed step (acidic media is beneficial for the C–H activation).

2-Acetamido benzophenone was prepared from aniline using the two step one-pot procedure, and compound **4a** was obtained in 68% yield (Scheme 2.). Methyl substituted acetanilides gave *N*-(2-benzoylphenyl)acetamides (**4b** and **4c**) in good yields (76% and 69% yield respectively), while the dimethyl product **4d** was obtained in 50% yield. The bulky isopropyl group in the *para* position did not affect the reaction significantly (55%) compared to methyl group. In the presence of halogens (F, Cl, Br) the sequential reaction also worked, and the appropriate products were isolated with 54%, 42% and 40% yield respectively after two reaction steps.

The reaction under the applied conditions readily tolerated the presence of a free hydroxyl group, and we obtained *N*-(2-benzoyl-4-(2-hydroxyethyl)-phenyl)acetamide (**4i**) in high yield (84%). The sequential reaction could be achieved in the



Scheme 2 Substrate scope of anilines. *Reaction conditions*: (a) step 1: acetanilide (1.0 mmol), SDS (0.05 mmol), water (4 mL), acetic anhydride (1.5 mmol) at RT; step 2: $Pd(OAc)_2$ (0.05 mmol), TFA (0.26 mmol), benzaldehyde (2.0 mmol), TBHP (2 mmol, 70 wt% in water), at RT, 24 h. (b) Step 1: acetanilide (1.0 mmol), SDS (0.075 mmol), water (4 mL), acetic anhydride (1.5 mmol) at RT; step 2: $Pd(OAc)_2$ (0.075 mmol), TFA (0.39 mmol), benzaldehyde (2.0 mmol), TBHP (2 mmol, 70 wt% in water), at 40 °C, 24 h. Yields of isolated product.



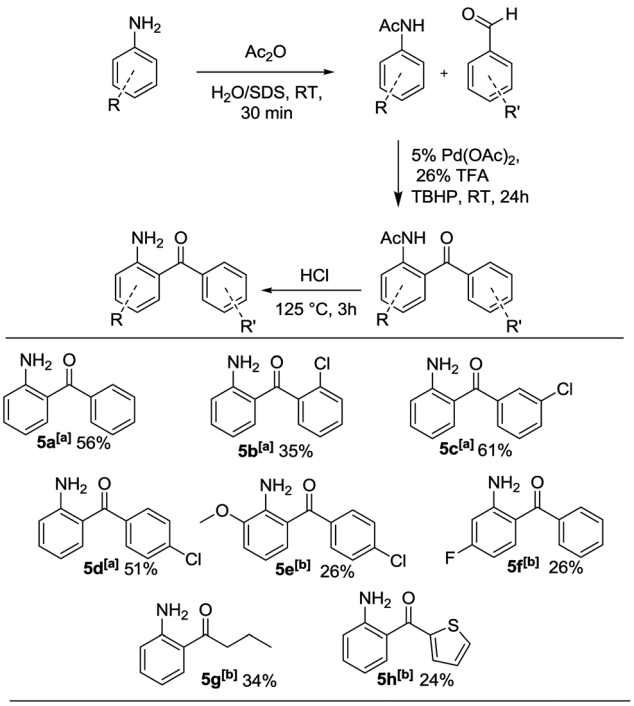
Scheme 3 *Reaction conditions*: (a) step 1: acetanilide (1.0 mmol), SDS (0.05 mmol), water (4 mL), acetic anhydride (1.5 mmol) at RT; step 2: $Pd(OAc)_2$ (0.05 mmol), TFA (0.26 mmol), benzaldehyde (2.0 mmol), TBHP (2 mmol, 70 wt% in water), at RT, 24 h. (b) Step 1: acetanilide (1.0 mmol), SDS (0.075 mmol), water (4 mL), acetic anhydride (1.5 mmol) at RT; step 2: $Pd(OAc)_2$ (0.075 mmol), TFA (0.39 mmol), benzaldehyde (2.0 mmol), TBHP (2 mmol, 70 wt% in water), at 40 °C, 24 h. Yields of isolated product.

presence of ester function on the aniline part and the appropriate benzophenone derivative (**4j**) was obtained.

Substituents on the aromatic ring of the aldehyde substrate slightly influenced the isolated yields of the product (yield varied in the range of 62–86%, Scheme 3.). *Ortho*, *meta* and *para* halogenated benzaldehydes, as well as methoxy benzaldehyde resulted in good yields (**4k–4p**). Aliphatic and heterocyclic aldehydes are also compatible with the reaction conditions, but their transformation required higher palladium catalyst loading (7.5 mol%) and 40 °C (**4q**, **4r**). Electron rich anilines such as *para* anisidine and 4-isopropyl aniline were also acylated in position 2 with substituted aromatic aldehydes after the protection of free amino group, and the appropriate products (**4s** and **4t**) were obtained with 33% and 36% yield.

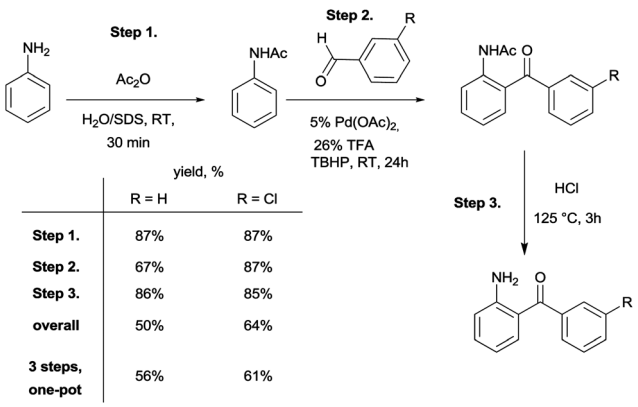
We have demonstrated that anilines are reasonable starting materials for the palladium catalyzed C–H acylation coupling under aqueous conditions in a two steps one-pot process at room temperature. The conditions of *N*-acylation of the free amino group and the cross-dehydrogenative coupling are compatible. Moreover, during the synthesis of more complex structures, the protecting group is usually removed after several synthetic steps providing the desired functional group in target molecules.

In our case, removal of the acetyl group from the amino moiety would provide substituted anilines. This hydrolytic cleavage is usually performed under acidic conditions, which is also compatible with our sequence. Therefore we aimed to extend our procedure with a hydrolytic reaction step to obtain amino benzophenones in a three step, one-pot reaction from anilines using acetyl group as a removable protecting and directing group for C–H activation.



Scheme 4 *Reaction conditions*: (a) step 1: acetanilide (1.0 mmol), SDS (0.05 mmol), water (4 mL), acetic anhydride (1.5 mmol) at RT; step 2: $Pd(OAc)_2$ (0.05 mmol), TFA (0.26 mmol), benzaldehyde (2.0 mmol), TBHP (2 mmol, 70 wt% in water), at RT, 24 h; step 3: 3.5 mL HCl (37 wt% in water), 125 °C. (b) Step 1: acetanilide (1.0 mmol), SDS (0.075 mmol), water (4 mL), acetic anhydride (1.5 mmol) at RT; step 2: $Pd(OAc)_2$ (0.075 mmol), TFA (0.39 mmol), benzaldehyde (2.0 mmol), TBHP (2 mmol, 70 wt% in water), at 40 °C, 24 h. Step 3: 3.5 mL HCl (37 wt% in water), 125 °C. Yields of isolated product.

Accomplishing the protection, coupling and deprotection in a row without the isolation of the intermediate products shortens the reaction time and produces less waste. For this reason, after the acylation of aniline (**1a**), and the palladium catalyzed cross dehydrogenative coupling of the formed acetanilide (**2a**) and benzaldehyde (**3a**), we treated the reaction mixture with 37% HCl at 125 °C. To our delight, complete hydrolysis took place in 3 hours providing the appropriate amino derivative of benzophenone (**5a**) and the desired compound was isolated with 56% yield. Next, we examined the substrate scope of the extended three steps sequence. Following the protection and palladium catalyzed step the final hydrolysis completed in 3 hours in all cases (**5a–5h**, Scheme 4.). Although, the yield varied in the range of 24–61% the three step one-pot process provide the desired product with the same efficiency compared to the step-by-step procedure.



yield, %	R = H	R = Cl
Step 1.	87%	87%
Step 2.	67%	87%
Step 3.	86%	85%
overall	50%	64%
3 steps, one-pot	56%	61%

Scheme 5 Comparison of step-by-step and one-pot processes.

In two cases, we compared the one-pot process to the reaction sequence with full isolation of the intermediate products (Scheme 5). Starting with aniline, we found that compound **5a** was obtained with 50% overall yield, while the one-pot process gave the product with similar efficiency (56%). A similar outcome was observed in the preparation of aminobenzophenone **5c**.

Conclusions

In summary, we developed new sequential methods for the synthesis of 2- acetamido or 2-amino benzophenone derivatives. These methods both include the protection of aniline derivatives followed by palladium-catalyzed cross dehydrogenative coupling of aldehydes under aqueous conditions at room temperature. After the C–H activation step the appropriate acetamido derivatives can be isolated or hydrolyzed in the same pot to obtain amino benzophenones, which provide simpler and faster synthetic routes to the desired target molecules. Three sequential chemical transformations without the isolation of each intermediate serve as a practical procedure, producing less waste, and requiring less energy and time for work up. All reactions were performed in water in the presence of SDS, which makes the method more attractive with regard to safety and economic aspects.

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