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Carbon−Hydrogen Bond Functionalization Approach for the Synthesis of Fluorenones and *ortho*-Arylated Benzonitriles

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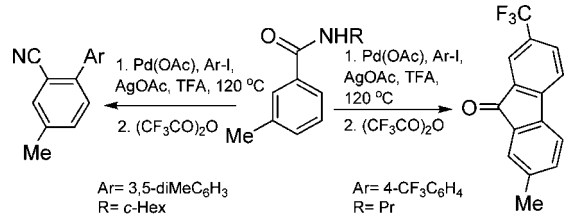

A sequence consisting of palladium-catalyzed benzamide *ortho*-arylation/reaction with $(CF_3CO)_2O$ was developed allowing a convenient one-pot synthesis of *ortho*-arylated benzonitriles and fluorenone derivatives. The outcome of this transformation is dependent on the amide *N*-alkyl substituent. Dehydration of *ortho*-arylated *N*-cyclohexyl-benzamides by $(CF_3CO)_2O$ results in efficient production of benzonitriles. In contrast, *o*-arylated *N*-propylbenzamides are converted to fluorenone derivatives.

o-Cyano-substituted biaryls are valuable pharmaceutical intermediates and are widely used in organic synthesis.[1] The biaryl units can be obtained using well-developed cross-coupling methods.[2] However, this requires both coupling partners to be functionalized. Often, starting materials for these coupling reactions need to be synthesized, lengthening the synthetic schemes. Coupling of a C−H bond with a carbon−leaving group bond would allow the use of simple starting materials.[3]

The first transition-metal-catalyzed C−H/C−halogen bond couplings were developed by Tremont, Liebeskind, and Ohta in the 1980s.[4] Recently many other examples utilizing this methodology have been reported. Both unfunctionalized and directing-group-containing substrates can be arylated by aryl halides, stannanes, boronates, or aryliodonium salts under palladium, rhodium, and ruthenium catalysis.[5] Our group has previously developed a general method for coupling directing-group-containing substrates with aryl iodides.[6] Anilides, benzamides, benzylamines, 2-arylpyridines, and benzoic acids can be efficiently arylated by employing this methodology.[7] Good functional group tolerance is usually observed.

Unfortunately, this method cannot be employed for benzonitrile *ortho*-arylation. Nitriles are known to slow down or even stop catalytic cycles as a result of strong binding of cyano group to transition metals.[8] An alternative is to use another directing group that can be transformed into cyano group after the arylation step.[9]

It is known that amides can be converted to nitriles by using strong dehydrating agents, for example, phosphorus oxychloride or thionyl chloride.[10] Catalytic dehydration of primary amides is known.[11] Mild conditions (trifluoroacetic anhydride, room temperature) can be employed to obtain a benzonitrile from a primary benzamide.[12]

We have shown that arylated anilides can be dehydrated to form phenanthridines by using trifluoroacetic anhydride reagent.[7f] We decided to apply this approach to the synthesis of *ortho*-arylated benzonitriles. In preliminary experiments, isopropyl benzamides were subjected to the standard arylation conditions[7c] followed by reaction mixture treatment with

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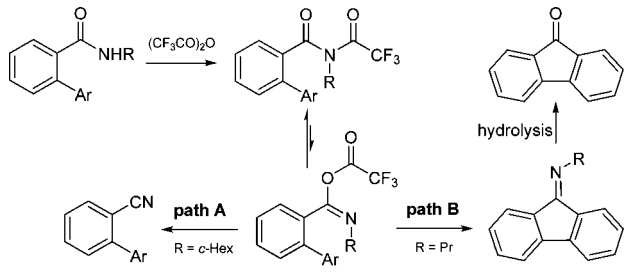
SCHEME 1. Proposed Reaction Path

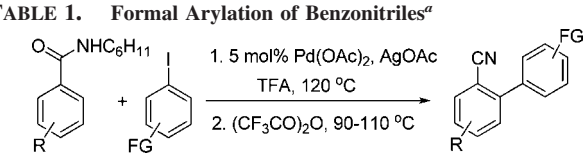


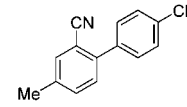
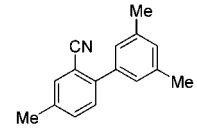
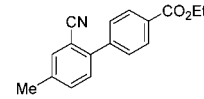
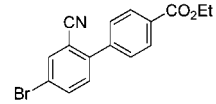
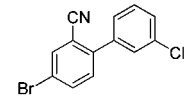
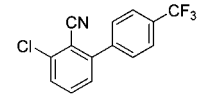
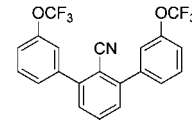
trifluoroacetic anhydride at 110 °C. This sequence resulted in the formation of a fluorenone and benzonitrile mixture.[13] The possible mechanism is presented in Scheme 1. After arylation and treatment of the reaction mixture with trifluoroacetic anhydride, an equilibrium mixture of *N*-trifluoroacetylamide and its *O*-trifluoroacetyl isomer[7f,14] is formed. If the R group is a secondary alkyl group that can form a stable carbocation, dealkylation of amide occurs and benzonitrile is formed as the major product (Scheme 1, path A). However, if the amide possesses a primary alkyl substituent, a stable carbocation cannot be formed, and electrophilic aromatic substitution results in the formation of fluorenone imine. Hydrolysis to fluorenone occurs during workup (Scheme 1, path B).

According to the above analysis, selective formation of benzonitriles can be achieved if the amide substrate contains a group capable of forming a carbocation with greater stability. Unfortunately, *t*-butyl amides are not stable under the arylation conditions. It has been reported that cyclohexyl cation is substantially more stable than isopropyl cation.[15] We were pleased to discover that cyclohexylamide derivatives formed nitriles selectively in most cases. Reaction of *N*-cyclohexyl-3-methylbenzamide with 4-chloroiodobenzene followed by treatment with trifluoroacetic anhydride resulted in 2-(4-chlorophenyl)-5-methylbenzonitrile formation in 65% yield (Table 1, entry 1). Other *ortho*-arylated benzonitriles can be obtained in moderate to good yields by employing the same conditions (Table 1). Electron-donating (entries 1−3) and -withdrawing (entries 4−6) groups can be present on benzamides. Both electron-rich (entry 2) and electron-poor (entries 1, 3−7) aryl iodides are reactive. However, when an electron-rich 3,5-dimethyliodobenzene was reacted with an electron-rich benzamide derivative, a fluorenone byproduct was isolated in 27% yield in addition to the desired nitrile. In all other cases, formation of fluorenone byproducts was not observed. *N*-Cyclohexylbenzamide can be diarylated, and upon treatment with trifluoroacetic anhydride an *ortho*-diarylated benzonitrile is obtained in a good yield (Table 1, entry 7). Chloride, bromide, ester, and ether groups can be present on both coupling partners.

As mentioned before, in preliminary experiments fluorenone side products were detected. Fluorenone is a key structure in some antitumor drugs,[16] natural products,[17] and compounds for

TABLE 1. Formal Arylation of Benzonitriles[a]



Entry	R	FG	Benzonitrile	Yield
1	3-Me	4-Cl		65%
2[b]	3-Me	3,5-diMe		54%
3	3-Me	4-CO_2Et		73%
4	3-Br	4-CO_2Et		56%
5	3-Br	3-Cl		72%
6	2-Cl	4-CF_3		84%
7	H	3-OCF_3		63%

[a] $Pd(OAc)_2$ (5 mol%), AgOAc (1.3−2.3 equiv), ArI (3−4 equiv), benzamide (1 equiv), TFA (0.7 mL), 120 °C; then $(CF_3CO)_2O$ (2−3 equiv), 90−110 °C. Yields are isolated yields. [b] 1,3,7-Trimethylfluorenone byproduct was isolated in 27% yield.

organic electronics.[18] There are two major synthetic approaches leading to fluorenones. First, Friedel−Crafts-type cyclizations (or their anionic equivalents) lead to fluorenones.[18a,c,19] The second methodology is based on carbon−carbon bond formation from benzophenone starting materials under Pschorr cyclization conditions or transition metal catalysis.[20] Other known methods for fluorenone synthesis require hazardous carbon monoxide[21] and highly reactive intermediates, for example, benzyne.[21a,22]

As discussed above, changing a *N*-cyclohexyl group to a *N*-propyl functionality should facilitate fluorenone core formation (Scheme 1, path B). Thus, 3-methyl-*N*-propylbenzamide

(13) Arylation of *N*-isopropyl-3-methylbenzamide with 4-chloroiodobenzene followed by treatment with trifluoroacetic anhydride resulted in formation of an 8:1 mixture of 2-(4-chlorophenyl)-5-methylbenzonitrile and 2-chloro-7-methylfluorenone (NMR analysis of crude reaction mixture). In contrast, arylation of the corresponding cyclohexylamide followed by reaction with trifluoroacetic anhydride afforded the nitrile exclusively (Table 1, entry 1). See the Supporting information for details.

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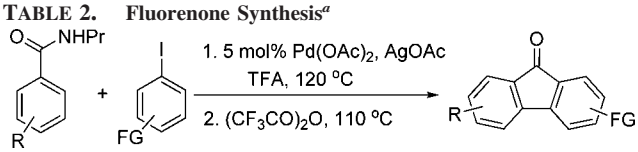
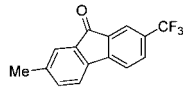
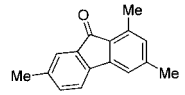
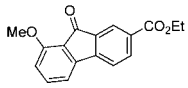
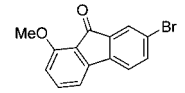
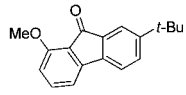
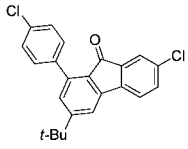
TABLE 2. Fluorenone Synthesis[a]



Entry	R	FG	Product	Yield
1	3-Me	4-CF_3		75%
2	3-Me	3,5-diMe		79%
3	2-MeO	4-CO_2Et		66%
4	2-MeO	4-Br		62%
5	2-MeO	4-*t*-Bu		62%
6	4-*t*-Bu	4-Cl		64%

[a] $Pd(OAc)_2$ (5 mol%), AgOAc (1.3−2.3 equiv), ArI (3−4 equiv), benzamide (1 equiv), TFA (0.7 mL), 120 °C; then $(CF_3CO)_2O$ (2−3 equiv), 110 °C. Yields are isolated yields.

was subjected to standard arylation conditions followed by reaction with trifluoroacetic anhydride at 110 °C. Fluorenone derivative was obtained as the only product in 79% yield (Table 2, entry 2). Other fluorenones can be synthesized in a similar fashion. Aryl iodides possessing electron-releasing (Table 2, entries 2 and 5) or electron-withdrawing (Table 2, entries 1, 3, 4, and 6) substituents can be used in this transformation, and fluorenones were isolated in 62−79% yields. Esters, ethers, and halogen atoms can be present on both coupling components. However, use of electron-poor benzamides was unsuccessful in our hands. Poor conversions were observed either during arylation or cyclization step. If *para*-substituted benzamides are used, after diarylation and treatment of reaction mixture with trifluoroacetic anhydride, 1-aryl-substituted fluorenones can be obtained (Table 2, entry 6).

In conclusion, we have developed a useful and convenient method for the synthesis of *ortho*-arylated benzonitriles and fluorenones starting from simple benzamides. The product yield and reaction scope in most cases is limited by the arylation step. Changing the alkyl substituent on the amide functionality makes it possible to fine-tune the reaction to obtain the desired product. Thus, *N*-propyl benzamides can be converted to fluorenones, whereas *N*-cyclohexyl benzamides afford benzonitrile derivatives. Good functional group tolerance is observed. Halogens, esters, and ethers are tolerated on benzamide and aryl iodide coupling components.

Experimental Section

General Procedure for Synthesis of Benzonitriles. A 2-dram vial was charged with substrate, $Pd(OAc)_2$ (5 mol%), AgOAc (1.3−2.3 equiv), aryl iodide (3−4 equiv), and trifluoroacetic acid (TFA) (0.5 mL). The resulting solution was heated at 120 °C for 0.5−4 h. Conversion was monitored by GC. After that, the reaction mixture was cooled to room temperature, and trifluoroacetic anhydride (2.0−3.0 equiv) was added. The vial was placed in oil bath (90−110 °C) for 1−3 h. The conversion was monitored by GC. After completion of the reaction, ether was added to the reaction mixture followed by filtration through a pad of Celite. Filtrate was washed twice with aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$. Solvent was removed by evaporation under reduced pressure (aspirator), and the residue was purified by flash chromatography.

2-(4-Ethoxycarbonylphenyl)-5-methylbenzonitrile (Table 1, entry 3). *N*-Cyclohexyl-3-methylbenzamide (152 mg, 0.7 mmol), $Pd(OAc)_2$ (7.8 mg, 0.035 mmol), AgOAc (152 mg, 0.91 mmol), and ethyl 4-iodobenzoate (580 mg, 2.1 mmol) were dissolved in TFA (0.5 mL). The resulting solution was heated for 40 min at 120 °C. After cooling to room temperature, trifluoroacetic anhydride (300 μL, 2.1 mmol) was added, and the reaction mixture was heated for 1.5 h at 90 °C. After completion, ether (5 mL) was added to the reaction mixture followed by filtration through a pad of Celite. Basic extraction and purification by flash chromatography (EtOAc/hexanes 1:9 to 1:7) gave 135 mg (73%) of a crystalline material, mp 133−134 °C (EtOAc/hexanes), $R_f = 0.42$ (EtOAc/hexanes 1:4). ^1H NMR (300 MHz, $CDCl_3$, ppm) δ 8.18−8.13 (m, 2H) 7.64−7.58 (m, 3H) 7.51−7.40 (m, 2H) 4.14 (q, 2H, $J = 7.2$ Hz) 2.45 (s, 3H) 1.42 (t, 3H, $J = 7.2$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 166.3, 142.6, 141.8, 138.7, 134.3, 134.0, 130.8, 130.14, 130.08, 129.0, 118.6, 111.4, 61.3, 20.9, 14.5. FT-IR (neat, cm^{-1}) υ 2224, 1716. Anal. Calcd for $C_{17}H_{15}NO_2$: C 76.96, H 5.70, N 5.28. Found: C 77.10, H 5.72, N 5.26.

General Procedure for Synthesis of Fluorenones. A 2-dram vial was charged with substrate, $Pd(OAc)_2$ (5 mol%), AgOAc (1.3−2.3 equiv), and aryl iodide (3−4 equiv). Trifluoroacetic acid (0.5 mL) was added, and the resulting solution was heated at 120 °C for 0.5−1 h. After completion of reaction (monitored by GC), the mixture was cooled to room temperature, and trifluoroacetic

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anhydride (TFAA) (2.0−3.0 equiv) was added. The vial was placed in oil bath (110 °C) for 1−4.5 h. The conversion was monitored by GC. After completion of reaction, ether or dichloromethane was added to the reaction mixture followed by filtration through a pad of Celite. The filtrate was washed twice with aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$. Solvent was removed by evaporation in vacuum, and the residue was purified by flash chromatography.

7-Methyl-2-trifluoromethylfluoren-9-one (Table 2, entry 1). 3-Methyl-*N*-propylbenzamide (124 mg, 0.7 mmol), $Pd(OAc)_2$ (7.8 mg, 0.035 mmol), AgOAc (140 mg, 0.84 mmol), and 4-trifluoromethyliodobenzene (571 mg, 2.1 mmol) were dissolved in TFA (0.5 mL). The resulting solution was heated for 40 min at 120 °C. After cooling to room temperature, trifluoroacetic anhydride (300 μL, 2.1 mmol) was added, and the reaction mixture was heated for 4.5 h at 110 °C. After completion, ether (5 mL) was added to the reaction mixture followed by filtration through a pad of Celite. Basic extraction and purification by flash chromatography (EtOAc/hexanes 1:17 to 1:13) gave 137 mg (75%) of yellow crystalline material, mp 125−126 °C (EtOAc/hexanes), R_f = 0.41 (EtOAc/hexanes 1/10). ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.89 (s, 1H) 7.73 (d, 1H, J = 7.9 Hz) 7.57 (d, 1H, J = 7.9 Hz) 7.52 (s, 1H) 7.47 (d, 1H, J = 7.7 Hz) 7.34 (d, 1H, J = 7.7 Hz) 2.41 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 192.5, 147.9, 140.9, 140.7, 135.8, 134.9, 131.7 (q, J_{C-F} = 5.3 Hz) 131.1 (q, J_{C-F} = 32.8 Hz) 125.6, 124.0 (q, J_{C-F} = 271.5 Hz) 121.35, 121.28, 121.1, 120.3, 21.6. FT-IR (neat, cm^{-1}) υ 1715. Anal. Calcd for $C_{15}H_9F_3O$: C 68.70, H 3.46. Found: C 68.44, H 3.41.

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Supporting Information Available: Detailed experimental procedures, characterization data for new compounds, and complete ref 12. This material is available free of charge via the Internet at http://pubs.acs.org.

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