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Metal-Free, Acid-Catalyzed *ortho*-Directed Synthesis of Anthranilic Acid Derivatives Using Carbodiimides

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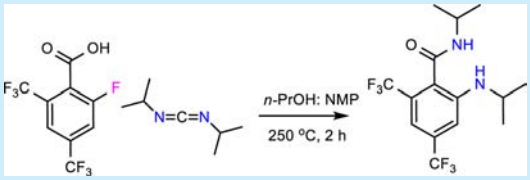
Supporting Information

ABSTRACT: One-pot syntheses of fluorescent *o*-aminobenzoates, *o*-aminopyridine carboxylates, and a 2′-amino-[1,1′-biphenyl]-2-carboxylic acid are described. Carbodiimides are used as the source of the 2-amino function which inserts onto an aromatic ring using S_NAr reaction conditions. This method proceeds regiospecifically with a range of 2-fluoroaromatic acids or esters bearing further aryl fluorine, trifluoromethyl, and cyano substituents.



Anthranilic acid features prominently in natural product structures[1] and finds application in fluorescence tags,[2] probes,[3] as an enabler in modern synthesis,[4] embedded in medicinal chemical structures[5a−c] (e.g., quinazolinones, benzodiazepindiones),[5d] as well as fragrances and dyes (e.g., indigo).[6] Given this broad utility, anthranilic acid synthetic methods are keenly pursued.

Modern synthetic routes to anthranilic acid have adopted palladium-catalyzed insertion of CO to create the carboxyl function[7] or C−H amidation.[8] Although these are undeniably powerful synthetic methods, they tend to display limited substrate scope and the necessity for several other metal additives that together curb their application suitability. Furthermore, the greening of chemical transformations seeks to avoid the use of metals and ligands to simplify the purification of chemical products. The Smiles rearrangement,[9a] an intramolecular S_NAr reaction requiring the synthesis of a 2-aryloxy-2-methylpropanamide precursor, was not possible for methyl salicylate[9b]—the prime substrate for anthranilic acid preparation.

Carbodiimides are versatile reactants in synthesis.[10] We have previously shown that carbodiimides are sufficiently nucleophilic to *ipso*-attack electron-poor aromatic ring systems, providing stable, spirocyclic Meisenheimer complexes in 100% atom-economy.[11] Recent examples have revealed that the carbodiimide function (RN═C═NR′) can be ruptured during the chemical transformation.[12]

We postulated that benzoic or other aromatic carboxylic acids, *ortho*-substituted with a suitable leaving group (e.g., F), may be able to undergo an S_NAr reaction via an *O*-isoacylurea intermediate to create a new regiospecific aryl C−N bond. This would constitute a new synthetic route to derivatized anthranilic acids, embracing the intense research arenas of C−F bond activation[13] and aryl C−N bond formation.[14] Comprehensively fluorinated aromatics are either commercially available, easily made,[15] or even created in situ,[16] thereby enhancing the synthetic potential of the S_NAr approach to valuable molecules, such as anthranilic acid. We present a new, metal-free synthetic method for regiospecific aryl C−N bond formation in an operationally simple one-pot route to anthranilic acids.

Our initial efforts focused on the optimization of 4-fluoroanthranilic acid derivative preparation since substrate acid **1f** provided a built-in barometer of both intra- (i.e., 2-fluoro) and intermolecular (i.e., 4-fluoro) S_NAr reactivity (Table 1). Alcohols were essential as a medium (entries 1−6; CAUTION: 2,2,2-trichloroethanol exploded under microwave irradiation) with DMAP as a base to remove the acidic HF byproduct (entries 7−12), which provided the product in low yields with diisopropylcarbodiimide (DIC), **2a** (entry 7, 23%). Yields with the other carbodiimides were even lower (entries 8−10) with **2f** (R = *t*-Bu), returning no yield (entry 11), potentially as a result of the steric bulk of their alkyl or aryl groups. Note the reaction with solid-phase-supported carbodiimide **2g**, which gave the solution-borne product as the only source of fluorescence, suggesting carbodiimide rupture during the course of the reaction, leaving a 2-cyclohexylamine substituent on the product (entry 12). Use of symmetrical carbodiimides, such as DIC, was preferred for simplicity. Proton sponge (1,8-bis-(dimethylamino)naphthalene, 1 equiv)[17] as additive revealed that effective sequestration of the HF byproduct prevented product formation, implying that DMAP merely acts as a proton repository in this reaction (entry 13) and that acid was required for the reaction to proceed to products. The addition of a Brönsted (*p*-tolylbenzenesulfonic acid (*p*-TSA); data not shown) or a Lewis acid ($Sc^{III}(OTf)_3$), indicative of esterification catalysis,[18] did not alter the reaction (entries 14−17), yet an increase in reaction temperature permitted by shifting to higher boiling alcohol solvents provided a gain in product yield (entries 14−16, 53%). A byproduct observed in this synthetic approach was the amide of the starting material, but since this could be

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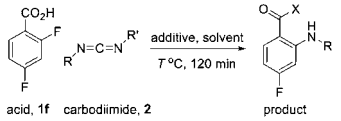
Table 1. Optimization of Reaction Conditions for the Synthesis of Anthranilic Acid Derivatives from 2,4-Difluorobenzoic Acid[a]



2a R = R' = *i*-Pr **2d** R = R' = cyclohexyl X = ester and 2° amide
2b R = R'=Bn **2e** R = R' = *p*-tolyl
2c R = Et, R' = *t*-Bu **2f** R = R' = *t*-Bu
2g solid-supported carbodiimide[b]

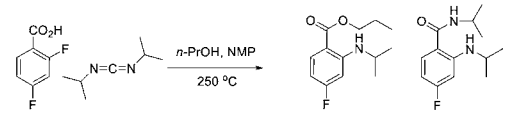
entry	carbodiimide (2 equiv)	additive (10 mol %)	solvent	*T* (°C)	product yield (%)
1	**2a**	DMAP	CH_3CN	100	0
2	**2a**	DMAP	acetone	100	0
3	**2a**	DMAP	THF	100	0
4	**2a**	DMAP	toluene	100	0
5	**2a**	DMAP	Cl_3CCH_2OH[c]	100	0
6	**2a**	DMAP	MeOH	100	20
7	**2a**	DMAP	EtOH	100	23
8	**2c**	DMAP	EtOH	100	17
9	**2d**	DMAP	EtOH	100	15
10	**2e**	DMAP	EtOH	100	10
11	**2f**	DMAP	EtOH	100	0
12	**2g**	DMAP	DCM/MeOH	100	16[d]
13	**2a**	proton sponge[f]	EtOH	100	0
14	**2a**	$Sc(OTf)_3$	*i*-PrOH	200	47
15	**2a**	$Sc(OTf)_3$	*i*-amylOH	230	53
16	**2a**	$Sc(OTf)_3$	$(HOCH_2)_2$	250	28[e]
17	**2a**	$Sc(OTf)_3$	*i*-BuOH	220	61
18	**2a**		*i*-BuOH	220	59
19	**2a**		EtOH	180	34
20	**2a**		*n*-PrOH/NMP	250	78

[a]Reaction conditions: **1f** (0.20 mmol). Sealed tube under microwave irradiation. [b]Novabiochem 855029 *N*-cyclohexylcarbodiimide, *N*′-methylpolystyrene, 1.9 mmol g^{-1} loading. [c]CAUTION: Use of 2,2,2-trichloroethanol resulted in an explosion under microwave irradiation. [d]Fluorescence isolated to solution-phase product. [e]Low yield due to difficult workup. [f]1,8-Bis(dimethylamino)naphthalene.

easily regenerated to **1** by hydrolysis, it was not viewed as a serious disadvantage (see S26). Removal of additive was not detrimental to the reaction outcome, thus simplifying the reaction mixture (entries 18 and 19) and suggested that the in situ formation of HF acts as a catalyst in this instance. In the same vein, construction of 4,5-disubstituted pyrazolopyrimidines by Wu et al. is a rare example of the use of acidic conditions (AcOH) in an S_NAr reaction.[19] As 4-fluoro substitution was not observed, a directed mechanism was invoked. Finally, evaluation of solvent compositions converged on a 1:1 (v/v) 1-propanol/NMP mixture. 1-Propanol has the highest boiling point of the completely water-miscible alcohols (bp = 97 °C), and NMP addition resulted in homogeneous and stable mixtures that allowed the swift attainment of high temperature (250 °C, 30 s) at low pressure (~7 bar) in a sealed microwave vial. This solvent mixture was easy to extract using an aqueous potassium hydrogensulfate-based liquid–liquid extractive workup procedure to provide pure products in high yield (entry 20, 78%).

Next, we explored the effect of reaction time and carbodiimide equivalents on product distribution (ester **3f** and amide **4f**) under our optimized reaction conditions (Table 2). We observed a relative increase in **3f** when DIC was increased from 5 to 10 equiv (entries 1 and 2). An increase in **4f** resulted when the

Table 2. Effect of Carbodiimide Equivalents and Reaction Time on Ester/Amide Product Ratio[a]



			yield[b] (%)	
entry	carbodiimide, **2a** (equiv)	reaction time (min)	ester	amide
1	5	120	31	69
2	10	120	43	57
3	5	180	19	81

[a]Reaction conditions: **1f** (0.20 mmol). Sealed tube under microwave irradiation. [b]Relative isolated yields.

reaction time increased from 120 to 180 min (entries 1 and 3). Together, these observations agree with our proposed reaction mechanism (Scheme S1). This four-component reaction involves initial *O*-isoacylurea formation followed by an intramolecular, *ortho*-directed S_NAr reaction of the *O*-isoacylurea onto the 2-fluoro substituent, yielding a bicyclic intermediate that collapses by HF-catalyzed Fischer esterification. The initially obtained ester can then be converted into the more stable secondary amide by reaction with the carbamate byproduct (Scheme S1). This is consistent with the observed requirements for alcohol and acid (Table 1) and also the observed ester/amide product distribution variations (Table 2). Previous *ortho*-directed S_NAr reactions effected annelation by the application of an aromatic ring-tethered nucleophile[20a] or a bis-nucleophile, such as hydrazine, yielding indazolones.[20b,c]

Subsequently, the substrate scope of acid **1** was investigated (Table 3). The quantity of carbodiimide **2** was fixed at 3 equiv as any more resulted in unreacted material remaining at the end of the experiment.

Our proposed mechanism requires 1 equiv of carbodiimide. However, more than 1 equiv of **2** was necessary to overcome wasting, presumably by hydration to the corresponding urea from solvent-based water.

Unsubstituted **1a** provided **3a** as an oil and **4a** as a solid in a moderate total yield of **3a** and **4a** (Table 3, entry 1, 46%). The 5-boronic-acid-derivatized analogue of **1a** also delivered the same products **3a** and **4a** in the same quantity and distribution (data not shown), pointing to quantitative deborylation under the effect of the acidic HF byproduct. *ortho*-Substitution with halogens other than fluorine (**1b–1d**) did not supply any products, emphasizing the necessity of a 2-fluoro substituent in this metal-free transformation (entries 2–4). The fluorine-substituted series gave **4** as the dominant product in good total yields of 72–84% (entries 5–8), although the 5-fluoro derivative did not perform well under these conditions (entry 7, 15%), inviting further study. Although **1h** (2,6-difluorobenzoic acid) presented the opportunity for disubstitution, this only proceeded to a small extent under our conditions (see S25). This may be a consequence of the first sterically challenging and potentially hydrogen-bonding isopropylamine substituent initially inserted during the course of this reaction. The UV–vis excitation–emission spectrum for **4f** in water displays a Stokes shift of 91 nm (S27). The trifluoromethyl-substituted series again gave **4** as the main product (entries 9–11, 62–95%) with the notable exceptions of 6-trifluoromethyl-substituted acids **1l** and **1m**, where esters **3l** and **3m** furnished the greater yield (entries 12 and 13). This is probably a consequence of the greater steric

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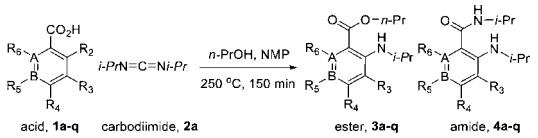
Table 3. Synthesis of Anthranilic Acid Derivatives



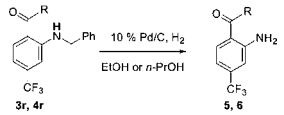
		substituents on acid, **1**								
entry	**1**[a]	R_2	R_3	R_4	R_5	R_6	A	B	**3** yield[b] (%)	**4** yield[b] (%)
1	**1a**	F							10	36[c]
2	**1b**	Cl							0	0
3	**1c**	Br							0	0
4	**1d**	I							0	0
5	**1e**	F	F						14	58[c]
6	**1f**	F		F					10	70[c]
7	**1g**	F			F				9	6
8	**1h**	F				F			9	75
9	**1i**	F	CF_3						21	55
10	**1j**	F		CF_3					20	75[c]
11	**1k**	F			CF_3				38	27[c]
12	**1l**	F				CF_3			38	24[c]
13	**1m**	F		CF_3		CF_3			56	22[c]
14	**1n**	F		CN					16	38
15	**1o**					F		N	76	8
16	**1p**	F		F			N		20	56
17	**1q**		F		F				0	95[d]
18	**1r**[e]	F		CF_3					16	70

[a] **1a–1q** reacted with **2a** (3 equiv) in a sealed tube under microwave irradiation at 0.2 mol L^{-1}. See S2 for structures of **1** and S3 for general experimental procedure. [b] Isolated yields (%) following workup, flash chromatography, and weighing. See S5–S17 for structures of **3** and **4**. [c] X-ray structure obtained. [d] Negative control reaction: product was *N*-isopropyl 3,5-difluorobenzamide. [e] **1r** was reacted with *N,N′*-dibenzylcarbodiimide **2b**.

constraint of the bulky CF_3 providing an obstacle to the ultimate formation of **4l** and **4m**. The 4-cyano acid **1n** provided a moderate 54% total yield (entry 14). The pyridine carboxylic acids **1o** and **1p** had contrasting ester/amide product distributions, with the nicotinic acid derivative **1o** being transformed almost entirely to ester **3o** (entry 15, 76%, total yield 84%), whereas the picolinic acid derivative **1p** provided mostly amide **4p** (entry 16, 56%, total yield 76%). We reasoned that protonation to create the pyridinium salts of **1o** and **1p** affected the path of the reaction in different ways depending on the relative carboxylic acid substitution pattern. As anticipated, the control experiment using 3,5-difluorobenzoic acid **1q** did not result in aromatic ring substitution products, with the *N*-isopropyl amide as the only product (entry 17, 95%).

Had **2f** participated in this novel reaction (Table 1, entry 11), deprotection of the resulting 2-*t*-butylaminobenzoic acid derivative would have been possible under standard TFA conditions.[21] However, by reacting *N,N′*-dibenzylcarbodiimide[22] with the high-yielding acid **1r** (Table 3, entry 18) followed by orthogonal hydrogenolytic deprotection,[23] the primary arylamine was unmasked, generating a traceless arylamine function in **5** and **6** (Scheme 1).

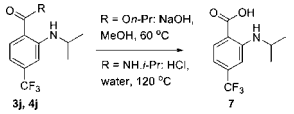
Scheme 1. Unmasking the 2-Arylamine Function[a]



[a] **3r**, **5**: R = O-*n*-Pr; **4r**, **6**: R = NH·Bn. X-ray structure for **6** was obtained.

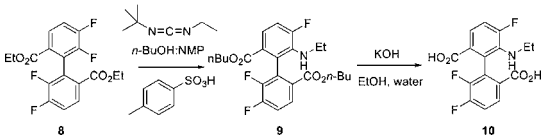
A remaining and necessary transformation converted **3** and **4** to carboxylic acid, which was achieved under classical hydrolysis conditions using **3j** and **4j** as typical examples to yield acid **7** (Scheme 2).

Scheme 2. Hydrolysis of Ester 3j and Amide 4j to Acid 7



The bicyclic intermediate proposed in our reaction mechanism (Scheme S1) suggested that it might be possible to extend the scope of the reaction to direct an intramolecular *N*-alkyl group transfer from one ring to the connected ring of a biphenyl molecule. Chemical **8**[24] was de-esterified in situ under *p*-TSA catalysis to the corresponding dicarboxylic acid, which then reacted with carbodiimide **2c** in a *n*-butanol/NMP solvent mixture to yield 2′-*N*-ethyl-substituted diester **9** as the major product (Scheme 3). Due to the spectroscopic complexity that

Scheme 3. Intramolecular Ring Transfer of an Alkylamine in a Biphenyl Molecule[a]



[a] **9** and **10** show diagnostic $^{19}F\{^1H\}$ NMR spectra as shown in Supporting Information.

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resulted from intermingled ethyl and *n*-butyl esters, **9** was saponified to diacid **10** (Scheme 3). NMR and MS analyses confirmed that one ethylamine group had been directed to the connected ring in a biphenyl system. The $^{19}F\{^1H\}$ NMR spectra of **9** and **10** were diagnostic of this novel intramolecular S_NAr reaction (S93 and S95). As seen with acid **1h**, the reaction only happens once within the experimental conditions employed. Although the involvement of biphenyl in S_NAr reactions is known in cases of annelation yielding fused tricycles,[25] to the best of our knowledge, this is the first example of this reaction.

In summary, we have prepared valuable anthranilic acids with electron-withdrawing substituents (fluorine, trifluoromethyl, and cyano) by the metal-free, regiospecific, and *ortho*-directed reaction of 2-fluoroaromatic acids and carbodiimides in good yield. This new reaction brings emphasis to the important area of metal-free aryl C−N bond formation[26,27] and complements the existing metal-catalyzed preparation of anthranilic acids where electron-donating substituents are preferred.[7,8] Further substrate scope and mechanistic and spectroscopic studies are ongoing in our laboratory and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures; proposed reaction mechanism; ^1H and ^{13}C NMR spectra; crystallographic data; chromatographic traces. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01160.

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Notes

The authors declare no competing financial interest.

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