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Synthesis of Novel Aryl and Heteroaryl Acyl Sulfonimidamides via Pd-Catalyzed Carbonylation Using a Nongaseous Precursor

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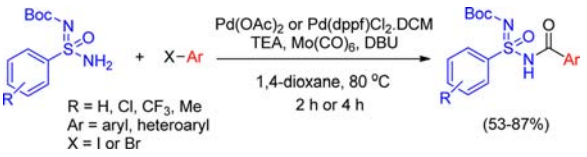
ABSTRACT



Hitherto unexplored aryl and heteroaryl acyl sulfonimidamides have been prepared through the development of a new Pd-catalyzed carbonylation protocol. This novel methodology, employing sulfonimidamides as nucleophiles and CO gas *ex situ* released from solid $Mo(CO)_6$ in a sealed two-chamber system, yields a wide range of carbamate protected acyl sulfonimidamides in good to excellent yields.

Sulfonimidamides, i.e. chiral analogues of sulfonamides in which one of the sulfonamide O-atom has been replaced by a N-atom, have received modest attention in the literature.[1] Since the pioneering report on sulfonimidamides from the Levchenko group in the early 1960s, the chemistry of these hexavalent sulfur derivatives has long been overshadowed.[2] Yet, in the past decade the Malacria and Dodd groups have investigated the reactivity and applications of sulfonimidamides in organic synthesis, mainly as a N-source for metal-catalyzed nitrene transfer reactions, for imination of sulfides using chiral nitrenes derived from sulfonimidamides, and for C–H insertion applications.[3] Moreover, Bolm et al. explored sulfonimidamides as ligands for transition-metal-catalyzed asymmetric synthesis and as chiral organocatalysts.[4] Also, a few reports, including patent applications, have revealed the usefulness of the sulfonimidamide functional group in bioactive molecules. These include synthesis of sulfonimidamide analogues of oncolytic sulfonylureas, sodium channel antagonists, pesticidal agents, and as transition state analogue inhibitors of aspartic acid metalloproteases.[5] Additionally, our group recently rationally explored sulfonimidamides as potential bioisosteres of

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sulfonamides in medicinal chemistry.[6] We observed increased solubility, decreased lipophilicity, and decreased plasma protein binding with the sulfonimidamide containing inhibitor, as compared to the corresponding sulfonamide.

As part of our current medicinal chemistry program, aiming to develop novel HCV NS3 protease inhibitors, we have had a long-standing interest in carboxylic acid bioisosteres.[7] Among several explored groups, the acyl sulfonamide group was proven to yield the most potent inhibitors for this target, a conclusion reflected in several of the clinical candidates encompassing the acyl sulfonamide group.[8] Our most recent inhibitors encompass aryl based acyl sulfonamides which allows for novel optimization possibilities.[9] Given the recent interest in sulfonimidamides as bioisosteres for sulfonamides, we became interested in exploring related acyl sulfonimidamides as carboxylic acid isosteres in our medicinal chemistry program. We envisioned that attachment of an acyl group to the sulfonimidamide should increase the acidity and thereby qualify this functionality as a potential carboxylic acid replacement. Besides, the stereogenic tetrahedral sulfur center and the additional points of diversity (i.e., the N-atom and S-atoms), offer additional means to tune potency and other properties of importance for drug design. Alteration of the stereochemistry at the chiral sulfur atom might also allow optimization to minimize off-target interactions, thus achieving greater selectivity toward drug targets. Altogether, these structural features offer unique optimization possibilities related to this functionality that are not feasible with other commonly used carboxylic acid bioisosteres, such as tetrazole and isoxazolone. Indeed, Pemberton et al. showed that the related cyclic analogue to the acyl sulfonimidamide possessed promising physicochemical properties including a slightly acidic proton.[10] In this respect we became interested in studying linear acyl sulfonimidamides. While evaluating methods for the preparation of this rather unexplored functional group through a methodology that would allow convenient access to a range of derivatives, we concluded that such derivatives might be available through a novel Pd-catalyzed carbonylation protocol utilizing a protected sulfonimidamide function as a hitherto unexplored nucleophile in this reaction.

We herein report, for the first time, the synthesis of carbamate protected aryl and heteroaryl acyl sulfonimidamides (compounds of pharmaceutical interest) through a Pd-catalyzed carbonylation process using *ex situ* generation of CO from $Mo(CO)_6$ as a solid source in a sealed two-chamber system.

Initially we screened reaction conditions on 4-iodo anisole as a model aryl halide, N-Boc protected sulfonimidamide **1** as the nucleophile, and 1,8-diazabicycloundec-7-ene (DBU)/triethylamine (TEA) as the base with 10 mol % of palladium acetate in 1,4-dioxane solvent. A quick screening of the effect of different CO reactants on the yield of N-Boc protected aryl acyl sulfonimidamides **2** and **3** was performed, and the results are summarized in Table 1. Gaseous CO at 75 psi in a pressure reactor afforded 51% yield at 80 °C (Table 1, entry 1). However, the problems associated with the invisible and odorless CO gas, such as high toxicity and high flammability, limit its use in modern carbonylative couplings.[11] As an alternative, CO-gas-free protocols that rely on solid or liquid reagents with the ability to release CO in situ have been developed as a safer, more convenient procedure.[12] In this regard, we also performed the amidocarbonylation of a sulfonimidamide nucleophile with molybdenum hexacarbonyl ($Mo(CO)_6$) as a solid CO source using microwave heating. However, the reaction was sluggish, possibly due to degradation of the formed product, which resulted in very poor yields of the isolated product after purification (Table 1, entries 2−3). Recently, Skrydstrup et al. developed a user-friendly two-compartment reaction setup for the Pd-catalyzed aminocarbonylation of aryl halides using *ex situ* generation of CO gas from a CO releasing source.[13] Successively, Larhed et al. used $Mo(CO)_6$ as the CO releasing source in a similar sealed two-chamber system.[14] We attempted this protocol for our amidocarbonylation of sulfonimidamide using the base triethylamine (TEA) in chamber A and 1,8-diazabicycloundec-7-ene (DBU) in chamber B. To our delight, product **2** was successfully isolated in 76% yield (Table 1, entry 5). It should be noted that the difference in yield reported between entry 1 and entries 4−5 (Table 1) was most probably related to the

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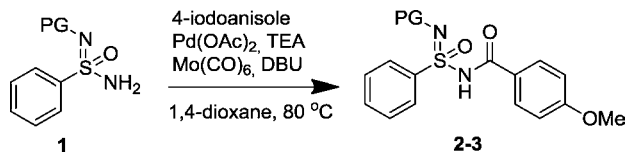
Table 1. Evaluation of Different CO Sources for the Pd-Catalyzed Carbonylation Reaction between Sulfonimidamides and 4-Iodoanisole[a]



1 2-3

entry	PG	CO source	product	time (min)	yield (%)[d]
1[a]	Boc	CO (75 psi)	**2**	45	51
2[b]	Boc	$Mo(CO)_6$	**2**	45	19
3[b]	CO_2Et	$Mo(CO)_6$	**3**	45	29
4[c]	Boc	$Mo(CO)_6$	**2**	60	69
5[c]	Boc	$Mo(CO)_6$	**2**	120	76

[a] Reaction conditions: sulfonimidamide (0.393 mmol, 1.0 equiv), 4-iodoanisole (0.984 mmol, 2.5 equiv), $Pd(OAc)_2$ (10 mol %, 0.1 equiv), DBU (0.984 mmol, 2.5 equiv), 1,4-dioxane (3.0 mL). [b] $Mo(CO)_6$ (0.589 mmol, 1.5 equiv) was used as a CO-releasing reagent, and the reaction mixture was heated by microwave irradiation. [c] *Ex situ* generation of CO gas from $Mo(CO)_6$ in a sealed two-chamber system (maximum expected CO pressure in the system is 20−30 psi).[14] Chamber A: sulfonimidamide (0.393 mmol, 1.0 equiv), 4-iodoanisole (0.984 mmol, 2.5 equiv), triethylamine (0.984 mmol, 2.5 equiv), $Pd(OAc)_2$ (10 mol %, 0.1 equiv) in dioxane (2.5 mL). Chamber B: $Mo(CO)_6$ (0.589 mmol, 1.5 equiv), DBU (0.984 mmol, 2.5 equiv) in dioxane (2.5 mL). [d] Isolated yields.

actual bases used. In entry 1, DBU was used as the base, in a single vial. In entries 4−5, using the two-compartment system, TEA was used as the base to regenerate Pd(0) species in chamber A and DBU to release CO gas in chamber B. Indeed, a similar yield (57%) was observed when we used DBU as the base in both chambers (*vide infra*, Table 2, entry 10), supporting the effect from bases on the yield. Using the two-chamber protocol, workup was simplified due to the absence of Mo-containing complexes formed during the reaction, and we did not observe any problems with product purification or with degradation under conventional heating. Furthermore, compounds containing aromatic nitro groups, which normally undergo reduction in the presence of $Mo(CO)_6$ in a single vial,[15] are now possible substrates for carbonylation reactions. Thus, we decided to perform the Pd-catalyzed carbonylation reactions in the two-chamber system for all aryl and heteroaryl acyl sulfonimidamides prepared throughout this work.

Next, the influence of various reaction parameters such as temperature, time, Pd-source, Pd-concentration, effects of solvents, and bases was examined using a two-chamber sealed vessel (Table 2). The optimization study concluded that the best yields (76%) were obtained with 1,4-dioxane as the solvent and triethylamine as the base over 10 mol % of $Pd(OAc)_2$ at 80 °C for 2 h. Reactions carried out at 60 °C or with reduced Pd-concentration to 5 mol % lowered the yields (Table 2, entries 2−3). Among the solvents studied, 1,4-dioxane, tetrahydrofuran, and dimethylformamide

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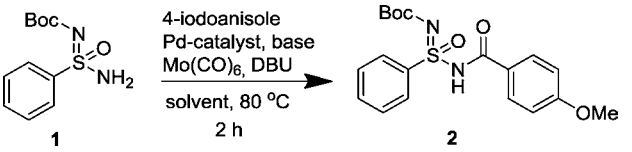
Table 2. Optimization of the Amidocarbonylation between Sulfonimidamides and 4-Iodoanisole[a]



1 2

entry	solvent	base	Pd-catalyst	yield (%)[d]
1	1,4-dioxane	TEA	$Pd(OAc)_2$	76
2[b]	1,4-dioxane	TEA	$Pd(OAc)_2$	54
3[c]	1,4-dioxane	TEA	$Pd(OAc)_2$	63
4	THF	TEA	$Pd(OAc)_2$	73
5	CH_3CN	TEA	$Pd(OAc)_2$	59
6	DMF	TEA	$Pd(OAc)_2$	68
7	toluene	TEA	$Pd(OAc)_2$	43
8	DCE	TEA	$Pd(OAc)_2$	53
9	1,4-dioxane	DIPEA	$Pd(OAc)_2$	46
10	1,4-dioxane	DBU	$Pd(OAc)_2$	57
11	1,4-dioxane	NaOAc	$Pd(OAc)_2$	26
12	1,4-dioxane	Cs_2CO_3	$Pd(OAc)_2$	39
13	1,4-dioxane	$NaHCO_3$	$Pd(OAc)_2$	13
14	1,4-dioxane	TEA	$Pd(PPh_3)_4$	72
15	1,4-dioxane	TEA	Pd/C	48

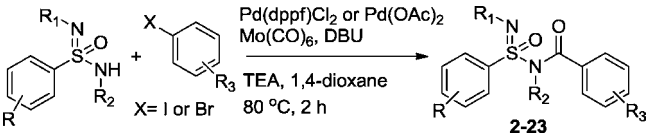
[a] Reaction conditions: Chamber A: sulfonimidamide (0.393 mmol, 1.0 equiv), 4-iodoanisole (0.984 mmol, 2.5 equiv), trietylamine (0.984 mmol, 2.5 equiv), $Pd(OAc)_2$ (10 mol %, 0.1 equiv) in dioxane (2.5 mL). Chamber B: $Mo(CO)_6$ (0.589 mmol, 1.5 equiv), DBU (0.984 mmol, 2.5 equiv) in dioxane (2.5 mL). [b] Reaction performed at 60 °C. [c] 5.0 mol % of $Pd(OAc)_2$ was used. [d] Isolated yields.

gave the best yields (entries 1, 4, 6). The use of a nonpolar solvent (i.e., toluene) resulted in lower yields (43%, entry 7). Organic bases were superior to inorganic bases, possibly due to the partial inhomogeneity of inorganic bases in the reaction mixture (entries 1, 9−10 vs 11−13). There was no further advantage in changing the Pd-source to $Pd(PPh_3)_4$, since a similar yield of product was provided as compared to using $Pd(OAc)_2$ (entries 1, 14). However, Pd loaded onto the carbon support (Pd/C) was less successful (48% yield, entry 15).

To establish the scope of amidocarbonylation, the optimized reaction conditions were then applied to a wide range of aryl iodides and bromides and various aryl sulfonimidamide nucleophiles to deliver corresponding protected acyl sulfonimidamides (Table 3). The effect of different N-protecting groups on the sulfonimidamide was studied, and no significant difference was observed when changing the protecting group from N-Boc **2** (76%) to N-Bz **4** (81%). However, the yield was reduced marginally when N-CO_2Et **3** (62%) was used as the protecting group on sulfonimidamide. Because of its comparatively easy removal N-Boc was selected in the forthcoming experiments.

Amidocarbonylation of N-Boc protected sulfonimidamides with aryl iodides proceeded with 10 mol % of $Pd(OAc)_2$ for 2 h. In contrast, aryl bromides required the use of 10 mol % $Pd(dppf)Cl_2$/DCM catalyst and a 4 h reaction duration to offer comparable yields to aryl iodides.[16] Different N-Boc protected sulfonimidamides were carbonylated with 4-iodoanisole, providing products in

Table 3. Synthesis of Aryl Acyl Sulfonimidamides[a]



prod.	R	R_1	R_2	R_3	X	yield (%)[b]
2a	H	Boc	H	4-OMe	I	76
2b	H	Boc	H	4-OMe	Br	73
3	H	CO_2Et	H	4-OMe	I	62
4	H	COPh	H	4-OMe	I	81
5	4-Me	Boc	H	4-OMe	I	74
6	4-Cl	Boc	H	4-OMe	I	67
7	4-CF_3	Boc	H	4-OMe	I	61
8	H	Boc	H	4-Br	I	75
9	4-Cl	Boc	H	4-Cl	I	78
10	4-Cl	Boc	H	2-Cl, 4-Cl	I	59
11a	H	Boc	H	H	I	72
11b	H	Boc	H	H	Br	69
12	H	Boc	H	4-Me	I	71
13a	H	Boc	H	4-CN	I	78
13b	H	Boc	H	4-CN	Br	74
14	H	Boc	H	4-F	Br	82
15	H	Boc	H	4-CF_3	Br	78
16	H	Boc	H	4-Ac	I	63
17	H	Boc	H	2-NO_2	I	53
18	H	Boc	H	3-NO_2	I	87
19	H	Boc	H	4-NO_2	I	78
20	H	Boc	H	4-CO_2Et	Br	76
21	H	Boc	H	4-Ph	Br	79
22[c]	H	Boc	H	3→4(−$CO(CH_2)_2CH_2$−)	Br	66
23	H	Boc	Me	4-OMe	I	13

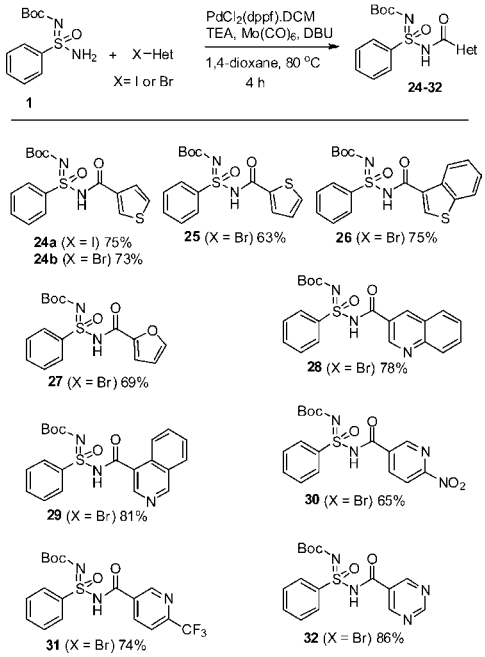
[a] Reaction conditions: Chamber A: sulfonimidamide (1.0 equiv), aryl halide (2.5 equiv), triethylamine (2.5 equiv), $Pd(OAc)_2$ (10 mol %) in dioxane (2.5 mL). Chamber B: $Mo(CO)_6$ (1.5 equiv), DBU (2.5 equiv) in dioxane (2.5 mL). For aryl bromides: Pd(dppf)Cl_2.DCM (10 mol %) was used as the catalyst, and reaction duration was 4 h. [b] Isolated yields. [c] 7-Bromo-3,4-dihydronapthalen-1(2*H*)-one used as aryl halide.

moderate to good yields (**5**–**7**). In general, a variety of functional groups were tolerated, and the reaction proceeded efficiently with *meta*- and *para*-substituted aryl halides. However, *ortho*-substitution on the aryl halide ring lowered the yield [**10** (59%) and **17** (53%)]. It is also worth noting that complete chemoselectivity for iodine over bromine and chlorine was achieved in the reactions (**8**–**10**). Furthermore, products derived from *o*-, *m*-, and *p*-iodonitrobenzenes (**17**–**19**) were isolated in excellent yields, which further demonstrate the advantage of using the two-chamber sealed system where CO gas is generated *ex situ* from $Mo(CO)_6$. Although the optimized protocol was high-yielding with all of the investigated aryl iodides and bromides, there seems to be a limitation using secondary sulfonimidamides since N-methylated **23** was isolated in only 13% yield.

Having established an excellent scope with aryl iodides and bromides, the usefulness of the protocol with heteroaryl halides as substrates was addressed (Scheme 1). Gratifyingly, the conditions optimized for aryl bromides provided moderate to good yields of heteroaryl acyl

(16) Aryl bromides gave a very poor yield (11%) when we used 10 mol% $Pd(OAc)_2$ catalyst.

Scheme 1. Synthesis of Heteroaryl Acyl Sulfonimidamide[a]



[a] Reaction conditions: Chamber A: sulfonimidamide (1.0 equiv), aryl halide (2.5 equiv), triethylamine (2.5 equiv), $Pd(dppf)Cl_2 \cdot DCM$ (10 mol %) in dioxane (2.5 mL). Chamber B: $Mo(CO)_6$ (1.5 equiv), 1,8-diazabicycloundec-7-ene (2.5 equiv) in dioxane (2.5 mL).

sulfonimidamide without further optimization. Scheme 1 depicts that the methodology is applicable to a wide range of heterocycles such as five-membered furan and thiophene, six-membered pyridine and pyrimidine, and fused systems (**26**, **28**–**29**).

In summary, we report a novel synthesis of linear and protected acyl sulfonimidamides, a rarely explored chemical group in organic/medicinal chemistry, by means of Pd-catalyzed carbonylations of aryl and heteroaryl iodides and bromides with sulfonimidamides as nucleophiles. The reaction shows high functional group tolerance and provides good to excellent yields of carbamate protected acyl sulfonimidamides. We anticipate great potential for this novel functional group as a unique carboxylic acid bioisostere. Next, we plan to explore the physicochemical properties of linear acyl sulfonimidamides and their deprotected analogues, as well as their pharmacological qualities.

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Supporting Information Available. Experimental procedures and full characterization data with copies of spectra for all the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.