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Two-Step Synthesis of α-Aryl-α-diazoamides as Modular Bioreversible Labels

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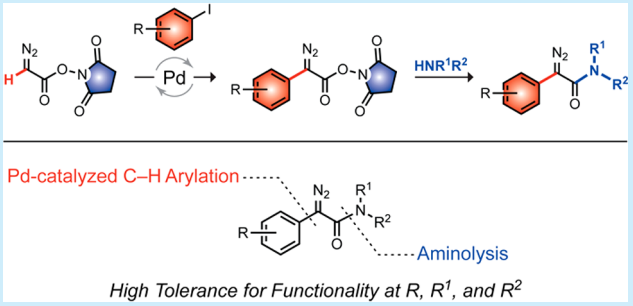
ABSTRACT: α-Aryl-α-diazoamides were synthesized in two steps under mild conditions. This expeditious route employs Pd-catalyzed C−H arylation of *N*-succinimidyl 2-diazoacetate to obtain *N*-succinimidyl 2-aryl-2-diazoacetates, followed by aminolysis. The ensuing diazo compounds can esterify carboxyl groups in aqueous solution, and the ester products are substrates for an esterase. The broad scope of the synthetic route enables the continued development of diazo compounds in chemical biology.

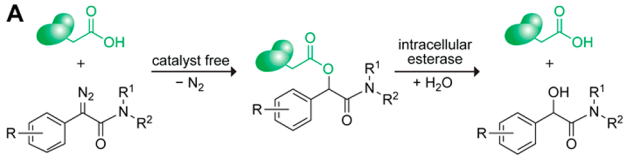


Since the discovery of diazomethane by von Pechmann in 1894,[1] diazo compounds have become important reagents in synthetic organic chemistry. Often, diazo groups are utilized via thermal, photochemical, or transition-metal-mediated carbenoid formation for constructing new C−C, C−O, or C−N bonds.[2] Recently, the utility of diazo compounds has been extended into the realm of chemical biology.[3,4]

Recent work has shown that α-aryl-α-diazoacetamides can esterify carboxyl groups in proteins (ribonuclease A,[5] green fluorescent protein,[6] and ribonuclease 1[7]), enabling their delivery across cellular membranes (Figure S1).[6,7] This strategy bears analogy to the use of ester prodrugs of small-molecule carboxylic acids.[8] The critical attribute of efficacious diazo compounds is their basicity,[9] which leads to abstraction of a proton from a carboxylic acid but not water and thereby to the esterification of carboxyl groups in aqueous solution.[5,10] Moreover, the ensuing esters are substrates for intracellular esterases.[6,7] This bioreversibility[11] provides a unique means to "cloak" protein carboxyl groups in a traceless manner (Figure 1A).

Although this application of α-aryl-α-diazoamides has demonstrated promise, synthetic accessibility (*e.g.*, a lengthy preparation time and a lack of scalability) has been a major deterrent to progress. Previously, such diazo compounds have been accessed via deimidogenation of the corresponding azide (Figure S1).[12] This approach has a high tolerance for functional groups, but access to the azide typically required lengthy low-yielding synthetic routes.[13] Additionally, the deimidogenation reaction was not compatible with 2-aryl-2-azidoacetamides containing bulky *N*-substituents.[6]

We sought a facile and general route to the modular α-aryl-α-diazoamide scaffold. Known synthetic routes can provide access to α-diazo carbonyl compounds. Most, however, focus on stable diazoketones, diazoesters, or aryl diazomethanes[14] and employ explosive diazo-transfer reagents, high temperature, or strong base,[3,15] conditions that can be incompatible with applications in chemical biology. Routes to α-aryl-α-diazoamides are underdeveloped and have limited substrate scope.[14,16] Their preparation and isolation is challenging



R′ Group	R = *p*-substituted EDG	Mild Aminolysis
O-Et (Wang, 2017)	Yes	No
O-*N*-phthalimide (Mendoza, 2019)	No	No
NR¹R² (Nelson, 2020)	No	—
O-*N*-succinimide (This work)	**Yes**	**Yes**

Figure 1. (A) Bioreversibility of protein esterification by an α-aryl-α-diazoacetamide. (B) Two-step synthesis of α-aryl-α-diazoacetamides. EDG, electron-donating group.

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because of insolubility and functional group incompatibility.[3,12,15,17]

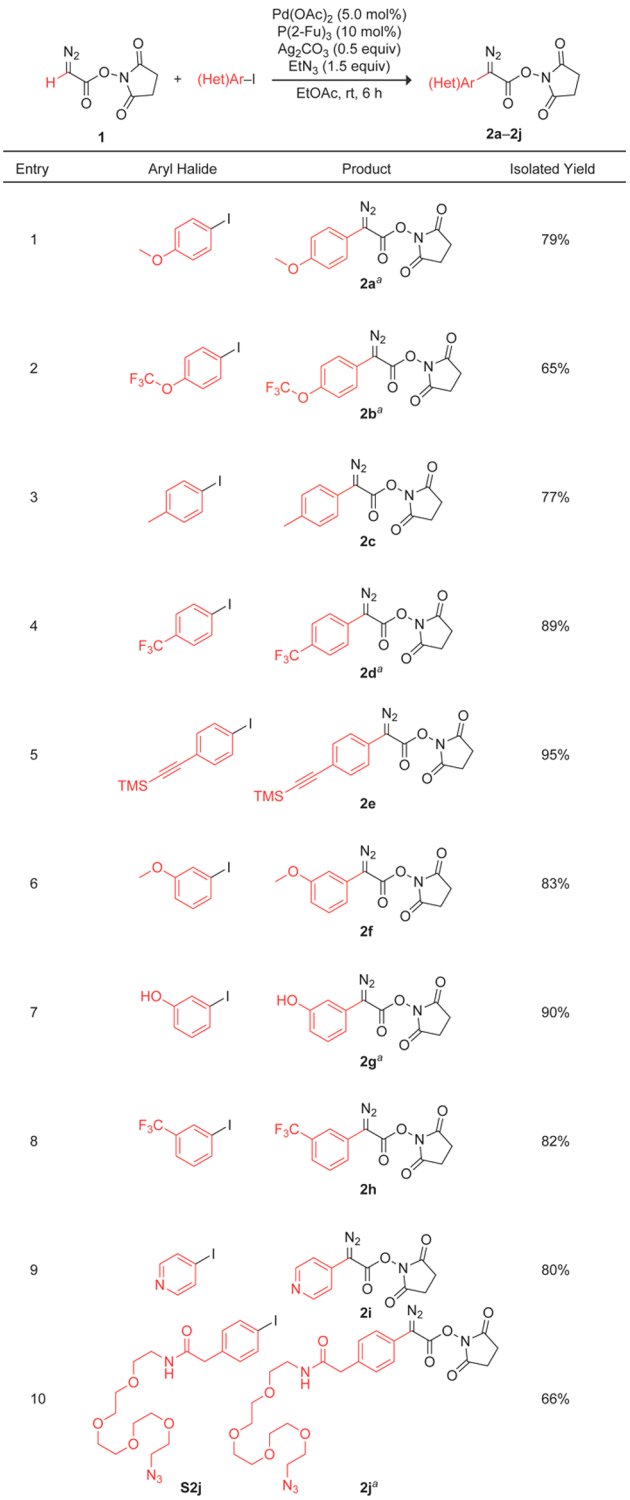
Here, we report on the mild, efficient, and versatile synthesis of α-aryl-α-amides in two steps from a commercially available[18] and highly scalable precursor, *N*-succinimidyl 2-diazoacetate (**1**).[19] Desired α-aryl-α-diazoamides are accessed via palladium-catalyzed C−H arylation followed by aminolysis under mild and safe conditions (Figure 1B). This route encompasses multiple benefits for applications in chemical biology: (1) facility, (2) broad applicability because of available building blocks (*i.e.*, aryl iodides and amines), and (3) compatibility with diverse functionality (e.g., azido and alkynyl groups) that can be useful for late-stage bioconjugation.

Metal-catalyzed C−H arylation in the presence of a diazo group has been reported only sporadically due to the undesired competitive formation of metal−carbene species (Figure 1B).[20] Wang and coworkers reported on the C−H functionalization of ethyl diazoacetate using $Pd(PPh_3)_4$.[20b,21] The product, however, required the use of a strong base or metal catalyst to effect amidation.[22] Mendoza and coworkers used another catalytic system, Pd(II) acetate and *tris*(2-furyl)phosphine ($P(2\text{-Fu})_3$), for the C−H arylation of *N*-phthalimidoyl diazoacetate to couple (hetero)aryl groups but encountered incompatibility with *p*-substituted electron-rich aryl groups (*e.g.*, 4-iodoanisole).[20c] Recently, Nelson and coworkers reported a suite of methods for the synthesis of α-diazoamides, including the C−H arylation of α-diazo *N*,*N*-disubstituted acetamides.[15] Similarly, this method failed in the coupling of electron-rich substrates (*e.g.*, 4-iodoanisole) and provided no examples of C−H arylation with α-diazo *N*-monosubstituted acetamides.

To access a large number of target compounds under mild conditions, we investigated diazo compound **1** as a coupling partner for C−H arylation. Diazo compound **1** has been used to install a diazo group via acyl transfer reactions with amines, phenols, thiophenol, and peptides.[19] We envisioned that the C−H arylation of diazo compound **1** could enable a rapid entry into more complex succinimidyl diazo compounds (**2**) and ultimately into diverse α-aryl-α-diazoamides (**3**).

We found that diazo compound **1** can undergo arylation with aryl iodides containing a wide variety of functional groups (Scheme 1). To do so, we prepared diazo compound **1** on a gram scale (Figure S2)[19,23] and employed a $Pd(OAc)_2/P(2\text{-Fu})_3$ catalytic system. Two additives, triethylamine (Et_3N) and silver carbonate (Ag_2CO_3), prevent product decomposition and scavenge iodide, respectively.[21,24] The reaction mixture was stirred in EtOAc at room temperature for 6 h. A range of aryl iodides, spanning electron-donating to -withdrawing *p*-substituted phenyl iodides, bulky *m*-substituted phenyl iodides, and a heteroaryl iodide, were subjected to the same reaction conditions. Notably, the electron-rich (**2a**), electron-neutral (**2c**), and electron-poor (**2d**) phenyl iodides all afforded high isolated yields (≥77%). Of the sterically hindered phenyl iodides, methoxy (**2f**) and trifluoromethyl (**2h**) functional groups at the *m*-position resulted in >80% isolated yields, whereas the smaller hydroxy group (**2g**) gave an even higher yield of 90%. We note too that 3-iodophenol (**2g**) proved to be orthogonal to the *N*-succinimidyl diazoester moiety, whereas 1-(4-iodophenyl)piperazine did not (Figure S11). The cross-coupling condition was compatible with heteroaryl substrate (**2i**) and a variety of fluoro groups, including trifluoromethoxy (**2b**), which is an important functional group for medicinal chemistry because of its high metabolic stability and cell permeability.[25] We effected C−H arylation in the presence of a TMS-protected alkynyl (**2e**) or azido (**2j**) group in 95 and 66% yields, respectively. Further, compound **2j** highlights a convenient means of diversification. This compound was accessed by a condensation reaction with 4-iodophenyl acetic acid. Lastly, we note that previously reported routes failed in arylation with 4-iodoanisole,[15] whereas our route provided **2a**

Scheme 1. Scope of the C−H Arylation of Diazo Compound 1



[a]Reaction conditions: 10 mol % $Pd(OAc)_2$ 20 mol % $P(2\text{-Fu})_3$.

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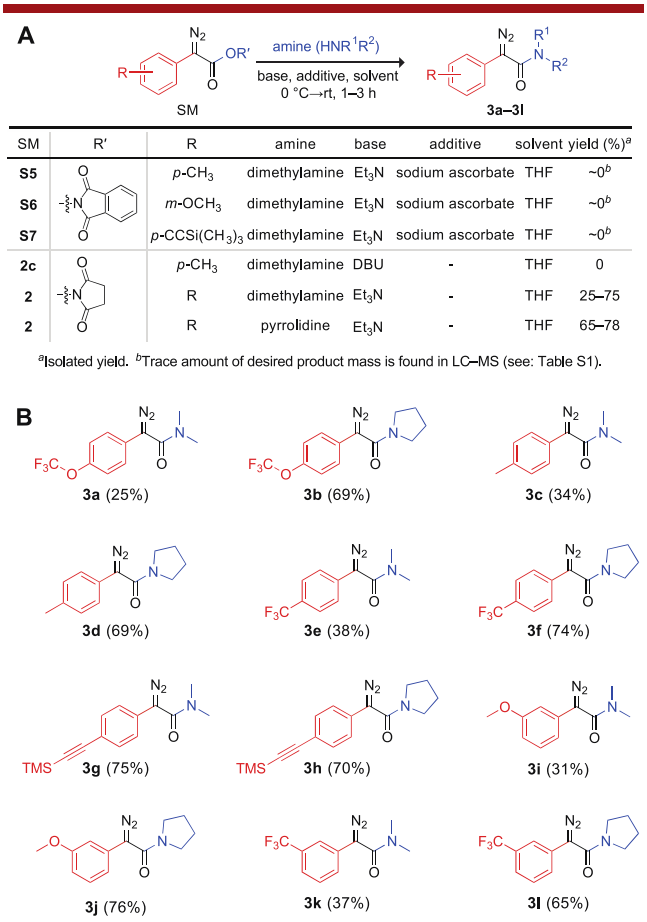
in 65% yield. Overall, we successfully demonstrated metal-catalyzed C−H arylation in the presence of *N*-succinimidyl and diazo groups, both of which will serve as important functionality for instilling diversity.

Next, we examined the aminolysis of representative *N*-succinimidyl *α*-aryl-*α*-diazoacetates **2b**−**2f** and **2h**. We first tested the aminolysis of analogous *N*-phthalimidoyl diazoesters **S5**−**S7**, which were synthesized by a method reported previously (Figure 2A).[20c] Those diazoesters yielded only a



SM	R′	R	amine	base	additive	solvent	yield (%)[a]
S5		*p*-CH_3	dimethylamine	Et_3N	sodium ascorbate	THF	~0[b]
S6		*m*-OCH_3	dimethylamine	Et_3N	sodium ascorbate	THF	~0[b]
S7		*p*-$CCSi(CH_3)_3$	dimethylamine	Et_3N	sodium ascorbate	THF	~0[b]
2c		*p*-CH_3	dimethylamine	DBU	-	THF	0
2		R	dimethylamine	Et_3N	-	THF	25–75
2		R	pyrrolidine	Et_3N	-	THF	65–78

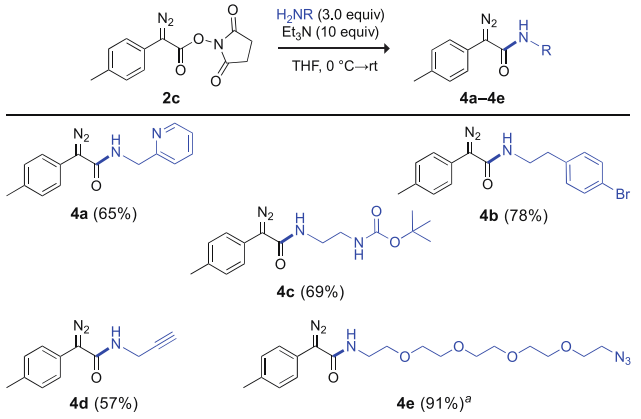
[a]Isolated yield. [b]Trace amount of desired product mass is found in LC–MS (see: Table S1).

Figure 2. (A) Aminolysis of *N*-succinimidyl *α*-aryl-*α*-diazoacetates with secondary amines. (B) Scope of the ensuing *N*,*N*-disubstituted *α*-aryl-*α*-diazoamides.

trace amount of diazoamide product based on liquid chromatography−mass spectrometry (LC−MS) analysis. Even after an extensive screening of reactant concentrations, solvents, and additives, aminolysis at *N*-phthalimidoyl diazoesters proved to be unattainable, possibly due to rapid decarboxylation (Table S1). An initial evaluation of aminolysis with **2c** showed that the use of 1,8-diazabicycloundec-7-ene (DBU) led to degradation, whereas Et_3N afforded the desired product (Figure 2A). In these reactions, a solution of the *N*-succinimidyl diazoester was treated with a secondary amine and Et_3N in tetrahydrofuran (THF) at 0 °C. The reaction mixture was stirred for 1−3 h at room temperature to yield the corresponding *α*-diazoamide (**3e**−**3l**) in up to 76% yield. An excess of Et_3N was used to prevent product decomposition. Most of the reactions showed quantitative conversion based on analysis with TLC (Figure S12). Due to their apparent degradation on silica, the isolated yields for diazoamide compounds **3a**, **3c**, **3e**, **3i**, and **3k** were low. Still, a wide range of aryl diazoesters was converted into *N*,*N*-disubstituted diazoamides.

Then, we demonstrated that the aminolysis of *N*-succinimidyl *α*-aryl-*α*-diazoacetates is also effective with various primary amines (Scheme 2). Those containing a

Scheme 2. Scope of the Aminolysis of *N*-Succinimidyl *α*-Aryl-*α*-diazoacetates with Primary Amines; Isolated Yields Are Reported



[a]Reaction conditions: 1.0 equiv of H_2NR.

pyridinyl (**4a**), arylhalo (**4b**), Boc-protected amino (**4c**), alkynyl (**4d**), or azido (**4e**) group displaced the *N*-hydroxysuccinimide moiety of **2c** to yield the desired *N*-monosubstituted diazoamides. Additional scope for this reaction includes 6 *N*-succinimidyl *α*-aryl-*α*-diazoacetates × 4 primary amines = 24 *α*-aryl-*α*-diazoacetamides (see: Scheme S1).

Having accomplished the facile synthesis of *α*-aryl-*α*-diazoamides, we turned our attention to their esterification of carboxylic acids. Specifically, we screened for the *O*-alkylation of five structurally diverse small molecules, pivalic acid, rhodamine B, coumarin-3-carboxylic acid, biotin, and HGluOMe, by three representative diazo compounds (**3h**, **3j**, and **3l**) in 1:1 acetonitrile:MES−NaOH buffer, pH 6.0, at 37 °C for 19 h (Figure S6). Each of the reactions was analyzed by LC−MS to quantify the esterified product as well as the hydrolyzed byproduct, *α*-aryl-*α*-hydroxyamide (Table S2). Though hydrolysis is unavoidable due to the excess of water, esterification was successful regardless of the steric and electronic nature of the carboxylic acid or diazo compound.

Finally, we tested the bioreversibility of esterification by our diazo reagents. As a model acid, we used $AcGluNH_2$ (**5**), which we derived from L-glutamic acid and which represents the most common residue for protein esterification[6] and 6.4% of the residues in human proteins.[26] In compound **5**, the N-terminal amino group is acetylated to prevent aminolysis of a side-chain ester, and the C-terminal carboxyl group is amidated to prevent main-chain esterification (Scheme S2). Compound **5** was treated with **3j** to yield ester **6**, which was then subjected to hydrolysis in the presence or absence of pig liver esterase (PLE) under biomimetic conditions at 37 °C (pH 5.8 for endosomes, pH 7.2 for the cytosol, and pH 8.0 for mitochondria).[27] Though stable at pH 5.8, ester **6** hydrolyzed readily at pH 8.0, even in the absence of PLE (Figure S10). The hydrolysis at pH 7.2 was, however, reliant on PLE (Figures 3 and S9). These data suggest that cellular esterases

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will catalyze the hydrolysis of a nascent ester to reveal the native carboxylic acid of a protein.

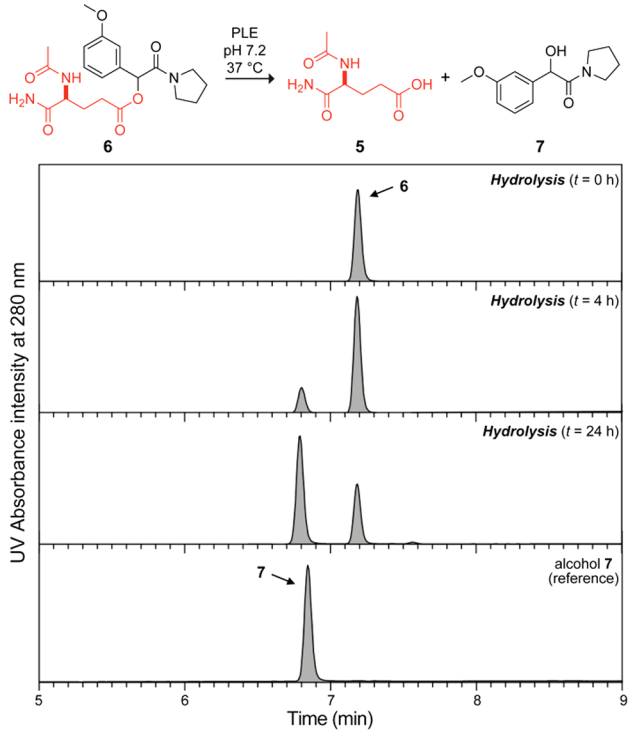

Figure 3. LC−MS analysis of the enzyme-catalyzed hydrolysis of γ-glutamyl ester **6** at pH 7.2 and 37 °C.

In conclusion, we demonstrated a facile two-step synthesis of α-aryl-α-diazoamides, which are modular reagents. This route will expedite the ongoing exploration of diazo compounds as reagents in chemical biology. We anticipate that the bioreversibility of our modification will enable applications in chemical biology, including the cellular delivery of proteins.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00793.

Experimental procedures, Tables S1−S3, Figures S1−S12, Schemes S1 and S2, NMR spectra, and additional compound characterization (PDF)

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Notes

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