Continuous Flow α-Arylation of *N,N*-Dialkylhydrazones under Visible-Light Photoredox Catalysis

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S *Supporting Information*

ABSTRACT: The first direct α-arylation of aldehyde-derived *N,N*-dialkylhydrazones with electron deficient aryl and heteroaryl cyanides under visible-light photoredox catalysis has been developed. Structurally complex α,α′-diaryl-*N,N*-cycloalkylhydrazones were obtained in moderate yields by repetition of the direct arylation protocol. A continuous-flow procedure for the preparation of α-aryl-*N,N*-dialkylhydrazones on a multigram scale has also been established.

Recent decades have seen visible-light photoredox catalysis (VLPC) emerging not only as a versatile and useful tool for functionalization of complex organic molecules and biologically active heterocycles but also for the discovery and development of novel synthetic methodologies.[1] In particular, late-stage, visible-light, photoredox-catalyzed chemoselective functionalization of $C(sp^3)$−H bonds adjacent to a nitrogen atom to $C(sp^3)$−$C(sp^2)$ bonds has recently attracted great interest due to the prominent role α-arylamines play in pharmaceuticals, with 8 of the 100 top-selling drugs containing this motif. In 2011, MacMillan et al. reported the direct arylation of α-amino $C(sp^3)$−H bonds via nucleophilic α-aminoalkyl radicals generated by photoredox-neutral-catalyzed aromatic substitution reaction of electron-deficient cyanoarenes with tertiary amines (Scheme 1a).[2] In a subsequent report, this $C(sp^3)$−$C(sp^2)$ bond-forming methodology was extended to α-amino acids in a direct decarboxylative arylation reaction via VLPC.[3] Doyle and MacMillan jointly reported the photoredox-nickel catalyzed direct decarboxylative arylation of α-amino acids with arylhalides, substantially expanding the $C(sp^2)$ pool of aryl coupling partners able to participate in this process.[4] Futhermore, an example of regioselective α,α′-diarylation of pyrrolidines has been recently described by combination of nickel, hydrogen-atom transfer (HAT), and dual Ni/VLPC.[5]

Hydrazone derivatives are considered valuable and versatile building blocks that enable a broad array of synthetic transformations[6] and display a wide range of biological activities.[7] Despite their rich reactivity, hydrazones have been scarcely explored in photoredox catalysis. Thus, Zhu et al. have recently reported on the visible-light photoredox-catalyzed $C(sp^2)$−H difluoroalkylation of aldehyde-derived hydrazones via an aminyl radical/polar mechanism as a novel way to synthesize substituted hydrazones (Scheme 1b).[8] This methodology was extended to the synthesis of fused pyrazoles[9] and dihydropyrazoles[10] in a sequential functionalization of $C(sp^2)$−

Scheme 1. VLPC in the Synthesis of α-Arylamines and Reactivity of Hydrazones under VLPC

H/$C(sp^3)$−H bonds of aldehyde hydrazones with 2,2-dibromo-1,3-dicarbonyls via VLPC (Scheme 1c).

Higly selective difluoro- and perfluoroalkylation of $C(sp^2)$−H bonds in aldehyde hydrazones has also been achieved in a gold-catalyzed visible-light photoredox reaction.[11] Pyrazoline

and pyridazine derivatives have been obtained in a cooperative TEMPO/photoredox catalytic process via a selective oxidative radical oxyamination of β,γ-unsaturated ketone derived hydrazones (Scheme 1d).[12] This process involved the direct conversion of a N−H bond into a N-centered radical. More recently, the C−H amidation of hydrazones via VLPC in a reductive single-electron transfer (SET) umpolung mechanism has also been reported.[13]

Within one of our research programs, we became interested in the multigram synthesis of structurally complex N,N-dialkylhydrazones of general structure **B** bearing an aromatic ring in α-position to the N−N bond. Inspired by the recent applications on VLPC with hydrazones and MacMillan's work on the direct arylation of α-amino C(sp^3)−H bonds, we hypothesized that hydrazones of general structure **A** could undergo direct arylation of α-amino C(sp^3)−H (Scheme 1e). Therefore, herein we describe the first examples of intermolecular arylation of α-amino C(sp^3)−H bonds in N,N-dialkylhydrazones under flow-VLPC. Iteration of the process allows for the preparation of α,α'-diarylation products **C** in moderate yields.

To verify our hypothesis, we selected hydrazone **1a** and 1,4-dicyano benzene (1,4-DCB, **2a**) as model substrates with 1 mol % of Ir(ppy)$_3$ as photocatalyst under irradiation at 455 nm with blue light-emitting diodes (LEDs). The reactions were carried out at 40 °C with LiOAc (2 equiv) as base and DMSO as solvent (Table 1). Our initial attempts varying **1a**/**2a**

Table 1. Evaluation of Conditions for the Direct Arylation of α-Amino C(sp^3)−H Bonds in Hydrazones[a]

entry	method	1a/2a	3aa, yield[b,c] (%)	3aa/4a[d]
1	batch	3.0:1	81	3:1
2	batch	1.5:1	89 (68)	8:1
3	batch	1.0:1	83	5:1
4[e]	batch	1.0:3	78	8:1
5[f]	batch	1.0:1	NR[h]	
6[g]	batch	1.0:1	NR[h]	
7[i]	batch	1.5:1	54 (38)	1:1
8[j]	flow	1.5:1	86 (64)	6:1
9[k]	flow	1.5:1	91 (75)	10:1

[a]Experiments carried out with 0.28 mmol of the limiting reagent at 0.25 M concentration. [b]LCMS yields with 1,3,5-trimethoxybenzene as internal standard. Isolated yields are shown in parentheses. [c]In general, isolated yields of hydrazones 3 were 15−20% lower than LCMS yields due to decomposition on silica gel. [d]LCMS ratio with 1,3,5-trimethoxybenzene as internal standard. [e]Reaction time 45 min. [f]Reaction run in the absence of light. [g]No Ir(ppy)$_3$. [h]NR: no reaction. [i]Experiment carried out with 3 mmol of **2a** at 0.25 M concentration; irradiation time 1 h. [j]Residence time 10 min. [k]Experiment carried out with 15.3 mmol of **2a** at 0.25 M concentration; residence time 10 min.

stoichiometry (Table 1, entries 1−4) were successful and the α-arylation product **3aa** was observed together with variable amounts of byproduct **4a**. The best result was obtained with 1.5 equiv of **1a** (Table 1, entry 2) resulting in 89% conversion and a **3aa**/**4a** ratio of 8:1. The direct arylation product **3aa** was isolated in 68% yield. The reaction did not occur in absence of

visible light or photocatalyst (Table 1, entries 5 and 6). Unfortunately, when the reaction was carried out on a larger scale (**2a**, 3 mmol) (Table 1, entry 7), a substantial decrease in conversion was observed and **3aa** could only be isolated in 38% yield.[14] As multigram quantities of α-arylated hydrazones were required for our purpose, we explored the possibility of translating the batch model conditions (Table 1, entry 2) to a continuous-flow process using the commercially available UV-150 photoreactor.[15] Optimization studies showed that subjecting a 0.25 M solution of **1a** (0.42 mmol), **2a** (0.28 mmol), LiOAc (2 equiv), and Ir(ppy)$_3$ (1 mol %) in DMSO to irradiation with 455 nm blue LEDs in a 10 mL coil with a residence time of 10 min resulted in 86% conversion and allowed for the isolation of **3aa** in 64% yield (Table 1, entry 8). To our delight, the results were comparable when the reaction was scaled up to 15.3 mmol of **2a** (Table 1, entry 9), and **3aa** was isolated in 75% yield.[16]

These continuous-flow VLPC conditions were extended to the set of hydrazones **1a−j** and cyanoaryls **2a-h** shown in Figure 1. The results obtained can be found in Table 2. N,N-
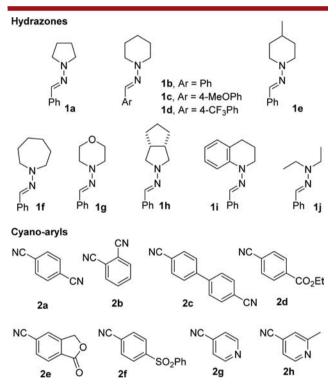

Figure 1. Hydrazones and cyanoaryls to study the reaction scope.

Cycloalkyl- (**1a-h**), N,N-arylalkyl- (**1i**), and N,N-dialkylhydrazones (**1j**) derived from benzaldehydes underwent α-arylation with a set of representative electron-deficient benzonitriles **2a−f** and 4-cyanopyridines **2g,h**, and the corresponding products **3** were obtained in good to moderate yields together with variable quantities of the corresponding α-cyano-substituted byproducts **4** (Table 2, entries 1−22). Interestingly, electron-withdrawing substituents in the hydrazone aromatic ring (Table 2, entry 4) are detrimental for the arylation reaction, while electron-donating groups (Table 2, entries 3 and 19) do not have strong influence on the reaction outcome when compared with the plain phenyl (Table 2, entries 1 and 16). Hydrazone **1e** containing a 4-methylpiperidine ring was α-arylated to yield **3ea** as a 1:1 mixture of cis/trans diastereoisomers (Table 2, entry 5).

Table 2. Scope of the Continuous Flow Direct α-Arylation of N,N-Dialkylhydrazones under VLPC[a]

entry	1	2	3, yield[b] (%)	4, yield[b] (%)
1[c]	1a	2a	3aa, 75	4a, 7
2[c]	1b	2a	3ba, 70	4b, 4
3	1c	2a	3ca, 72	4c, 11
4	1d	2a	3da, 22	4d, 10
5	1e	2a	3ea, 70[d]	traces
6	1f	2a	3fa, 75	4f, 22
7	1g	2a	3ga, 60	4g, 17
8	1h	2a	3ha, 80	traces
9	1j	2a	3ja, 70	4j, 6
10	1a	2b	3ab, 70	4a, 12
11	1a	2c	3ac, 73	traces
12[e]	1a	2d	3ad, 63	4a, 11
13	1a	2f	3af, 68	4a, 11
14[f]	1a	2g	3ag, 70	4a, 9
15[g]	1a	2h	3ah, 51	traces
16	1b	2d	3bd, 56	4b, 15
17	1b	2e	3be, 50	4b, 15
18[f]	1b	2g	3bg, 51	4b, 28
19	1c	2d	3 cd, 60	4c, 15
20[h]	1h	2d	3hd, 57	4h, 4
21[i]	1i	2d	3id, 55	traces
22[i]	1i	2g	3ig, 60	traces

[a]Experiments carried out with 0.40 mmol of the cyanoaryl **2** at 0.25 M concentration. [b]Isolated yields. [c]Experiment carried out with 10.6 mmol of **2a** at 0.25 M concentration. [d]Yield of a 1:1 mixture of *cis/trans* diastereoisomers. [e]Experiment carried out with 15.3 mmol of **2d** at 0.25 M concentration. [f]Residence time 30 min. [g]Residence time 40 min. [h]Experiment carried out with 6.22 mmol of **2d** at 0.25 M concentration. [i]Residence time 60 min.

Interestingly, α-arylation of the bicyclic hydrazone **1h** was diastereoselective and only compounds **3ha** and **3hd**, where the aryl group is in *trans* disposition with the fused cyclopentyl ring, were obtained (Table 2, entries 8, 20).

A second aryl group could be incorporated in α′-position of the hydrazone cyclic amine moiety by simple repetition of the photoredox catalytic process. Thus, hydrazones **3ad**, **3ag**, and **3hd** were selectively arylated in the α′-position with different cyano aromatics **2** under the VLPC continuous-flow reaction conditions shown in entry 8 of Table 1. For this second arylation, 2 mol % of photocatalyst, higher temperature, and longer residence times were needed (Scheme 2). In the case of **3ad** and **3ag**, the corresponding products **3ada**, **3adb**, **3adg**, and **3agh** were obtained with moderate yields and *cis* diastereoselectivity ratios up to 9:1. A fourth stereocenter was introduced in hydrazone **3hd** by reaction with 1,2-dicyanobenzene **2b** where the resulting product **3hdb** was obtained in 61% yield as a single diastereoisomer.[17]

A plausible mechanism is outlined in Scheme 3, where an initial SET from the excited-state form *Ir(III) of the iridium photocatalyst to the cyanoarene **2a** to form the radical anion **7** takes place. The oxidized Ir catalyst Ir(IV) then undergoes a

Scheme 2. Direct α′-Arylation of α-Arylhydrazones 3ad, 3ag, and 3hd VLPC

3ada, Ar[1]= 4-CO₂EtPh, Ar[2] = 4-CNPh (55%, *cis/trans* 9:1)
3adb, Ar[1]= 4-CO₂EtPh, Ar[2] = 2-CNPh (57%, *cis/trans* 2:1)
3adg, Ar[1]= 4-CO₂EtPh, Ar[2] = 4-Py (58%, *cis/trans* 1.3:1)
3agh, Ar[1]= 4-Py, Ar[2] = 2-Me-4-Py (42%, *cis/trans* 1.3:1)

Scheme 3. Proposed Mechanism

new SET process with hydrazone **1a** forming the radical cation **5**, and the Ir(III) species that initiates the photocatalytic cycle. Deprotonation of **5** with LiOAc followed by radical−radical coupling of the formed α-amine radical **6** with **7** results in the coupled product **8**. Aromatization of **8** with loss of CN⁻ renders the α-arylation product **3aa**.[18] The α-amino alkyl radical **6** can also undergo a SET event and get oxidized by an Ir(IV) species to form the iminium intermediate **9**. Reaction of **9** with the CN⁻ group coming from **8** would explain the formation of byproduct **4a**.

In summary, the first intermolecular α-arylation of aldehyde-derived N,N-diakylhydrazones with electron-deficient arylcyanides has been described. The reaction occurs under VLPC, and an efficient flow-chemistry protocol leading to the corresponding α-arylated products has been developed. The introduction of a second aryl group in α′-position was achieved with complete regioselectivity by simple repetition of the protocol, leading to structurally complex hydrazone derivatives.

■ **ASSOCIATED CONTENT**

ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00117.

Experimental procedures, a comparison between batch and continuous flow protocols, and spectral data for the new compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ DEDICATION

Dedicated to the memory of Prof. José Barluenga.

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(15) Reactor coil: 10 mL volume with an internal bore of 1.3 mm and a wall thickness of 0.15 mm. Further information about the Vapourtec photoreactor can be found at www.vapourtec.com.

(16) The hydrazone **3aa** was hydrolyzed to the corresponding hydrazine derivative **10** under standard conditions. Hydrazine **10** was subsequently reduced to the amine derivative **11**, applying standard methodology. For additional details, see the Supporting Information.

(17) Only traces of the corresponding α'-cyano derivative side product could be observed by LCMS analysis.

(18) Additionally, it cannot be ignored that the radical **6** could be formed via sequential SET reaction from the excited-state form *Ir(III) to the sp^2 carbon of hydrazone **1a** to form an intermediate α-amino radical anion that then undergoes a 1,4-hydrogen-atom transfer (HAT) event. For SET events on imine sp^2 carbons, see: (a) Hager, D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2014**, *136*, 16986. For 1,4-HAT reaction paths see: (b) Nechab, M.; Mondal, S.; Bertrand, M. P. *Chem.—Eur. J.* **2014**, *20*, 16034.