

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

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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.

R ecent 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(sp³)-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 photoredoxnickel 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 $\alpha_{,}\alpha'$ -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 transformations⁶ 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 pyrazoles⁹ and dihydropyrazoles¹⁰ in a sequential functionalization of $C(sp^2)$ -



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

Previous work



 $H/C(sp^3)$ -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

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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 1,4dicyano 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(sp³)-H Bonds in Hydrazones^{*a*}

\square	1,4-DCB 2	а		\frown
N N N	Ir(ppy) ₃ (1 m LiOAc (2 ec	iol %) luiv)		
Ph 1a	455 nm blue DMSO, 40 °C	LEDs , 30 min	Ph 3aa	Ph 4a
entry	method	1a/2a	3aa , yield ^{<i>b,c</i>} (%)	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. ^{*s*}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 electrondonating 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	of
N,N-Dialkylhydrazones under VLPC ^a	

	Ar ¹ -CN, 2			
R ²	² lr(ppy) ₃ (1 mol	%)	R ²	R ²
R ¹	LiOAc (2 equ	iv)	\mathbb{R}^1	\mathbb{R}^1
N		,	N Ar ¹	``Ń ℃N
N			_Ń +	Ń
År 1	455 nm blue LE	Ds	År 3	År 4
	DMSO, 40 °C, 1	0 min	AI	Ai -
entry	1	2	3 , yield ^b (%)	4, yield ^b (%)
1 ^c	la	2a	3 aa, 75	4 a, 7
2 ^{<i>c</i>}	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	4 g, 17
8	1h	2a	3ha , 80	traces
9	1j	2a	3ja , 70	4 j, 6
10	la	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>i</i>}	1i	2d	3id, 55	traces
22 ⁱ	li	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. ^{*c*}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



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.

CN

8

Ρh

In summary, the first intermolecular α -arylation of aldehydederived *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 -aryltated 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.or-glett.7b00117.

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

2a

3aa

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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 sp² 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 sp² 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.