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Benzhydrylamines via Base-Mediated Intramolecular sp^3 C-Arylation of *N*-Benzyl-2-nitrobenzenesulfonamides—Advanced Intermediates for the Synthesis of Nitrogenous Heterocycles

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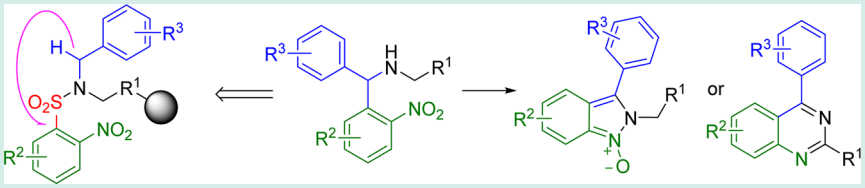
Supporting Information



ABSTRACT: *N*-Benzyl-2-nitrobenzenesulfonamides underwent base-mediated intramolecular arylation at the benzyl sp^3 carbon to yield benzhydrylamines. The presence of electron withdrawing groups on the aromatic ring of the benzyl group was required to facilitate the C-arylation. Unsymmetrically substituted benzhydrylamines are advanced intermediates toward nitrogenous heterocycles, as exemplified in the syntheses of indazole oxides and quinazolines.

KEYWORDS: *arylation, benzhydrylamine, C−C bond formation, heterocycle, indazole oxide, nitrobenzenesulfonamides, quinazoline*

INTRODUCTION

Fukuyama alkylation of 2- or 4-nitrobenzenesulfonylamides (Nos-amides) is recognized as a versatile and efficient route for the synthesis of secondary amines.[1,2] Using Nos-Cl to introduce a Nos protecting/activating group is simple; alkylation can be accomplished using electrophiles or alcohols; and removal of the Nos group from secondary amines using sulfur nucleophiles is straightforward. The solid-phase synthesis particularly benefited from this reaction sequence as all three steps proceeded with excellent conversion, and the isolation of resin-bound intermediates took only minutes.[3−5] However, the Nos group can not only serve as a protecting/activating group but also provide access to diverse nitrogenous heterocycles.

We have previously reported the solid-phase synthesis of 2*H*-indazole-1-oxides **A** (Scheme 1) via tandem carbon−carbon and nitrogen−nitrogen bond formation.[6,7] The key transformation involves C-arylation through a DBU-mediated Smiles-type rearrangement of 2-Nos-amides. This finding prompted us to further explore this chemical route and apply C-arylation to the synthesis of diverse heterocycles including pyrazino[1,2-*b*]indazoles[7] **B**, 2-(2-amino/hydroxyethyl)-1-aryl-3,4-dihydropyrazino[1,2-*b*]indazole-2-iums that cyclized to fused polycyclic heterocycles **C**,[8] and 2,3-dihydro-1*H*-imidazo-[1,2-*b*]indazoles **D** that resulted from rearrangement of **C**.[9] Base-catalyzed ring expansion of 2*H*-indazole-1-oxides prepared using Gly as the source of the primary amine yielded high purity quinazolines **E**.[10] An analogous C-arylation of a C$^\alpha$ amino acid carbon was also reported using 4-Nos derivatives; however, in this case, the synthesis stopped at C-alpha-aryl amino acid stage.[11,12]

Thus, far, we have exploited the C-arylation of *N*-(2-arylethyl-2-oxo) and *N*-(2-methoxy-2-oxoethyl) derivatives prepared through the alkylation of polymer-supported 2-Nos-amides with bromoketones and bromoacetates. In this contribution, we expanded our work and addressed its potential for the Nos-amide-based intramolecular C-arylation of benzyl sp^3 carbons. The arylated compounds are advanced intermediates for the synthesis of diverse nitrogenous heterocycles. An "advanced intermediate" here refers to a substrate with two or three diversity positions that can be used to synthesize structurally unrelated molecular scaffolds through modification of the peripheral substituents or by changing the reaction conditions. The strategy is exemplified in the syntheses of aryl derivatives of indazole oxides and quinazolines, derivatives not accessible by our previous syntheses.[6,10] Synthesis of 3-arylindazole oxides using a different synthetic strategy has already been reported.[13]

Numerous methods for arylation of the sp^3 carbon of benzylamine have been developed, which illustrates the general interest in this series of compounds as final products or intermediates in heterocyclic synthesis. Dastbaravardeh and co-workers have described the arylation of benzylamines with

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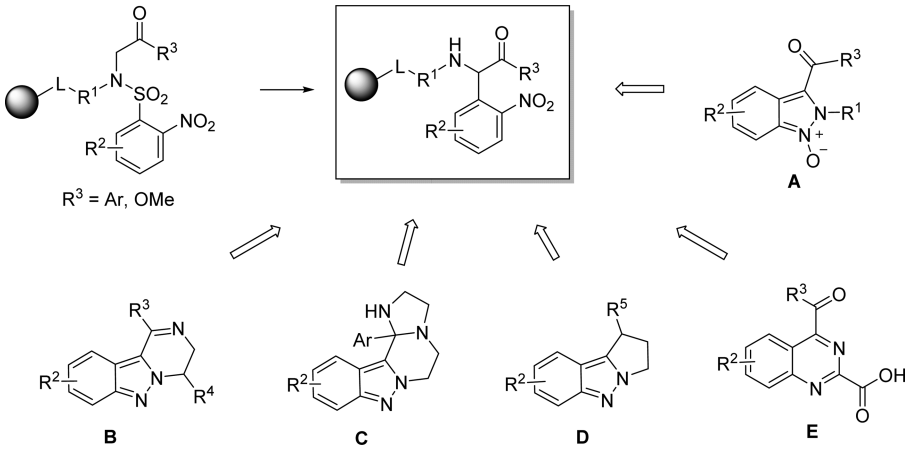
Scheme 1. Nitrogenous Heterocycles from 2-Nitrobenzenesulfonamides



arylboranes under Ru catalysis;[14] McGrew and co-workers developed a transition-metal-catalyzed cross coupling of aryl triflates for the enantioselective functionalization of the benzyl C−H bond;[15] Clayden and co-workers prepared substituted diarylmethylamines by the stereospecific intramolecular electrophilic arylation of lithiated ureas;[16] and photoredox-catalyzed C−H arylation was discovered through random reaction screening.[17] Direct sp^3 arylation of tetrahydroisoquinolines and isochromans via 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) oxidation has also been reported.[18] To the best of our knowledge, the synthesis of benzhydrylamine via the base-mediated sp^3 carbon arylation of *N*-benzylsulfonamides has not been previously reported.

RESULTS AND DISCUSSION

Design of Model Compounds. Figure 1 presents a generic structure of 2-nitrobenzenesulfonamides **1** amenable to

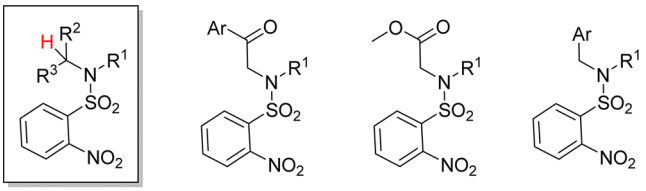


Figure 1. Structures of model compounds.

base-mediated intramolecular arylation. The key structural element is the presence of an acidic proton on the alpha-carbon. We have already described the C-arylation and subsequent formation of nitrogenous heterocycles from substrates **2** (structure **1** with R^2 = CH_2−CO−Ar and R^3 = H) and **3** (structure **1** with R^2 = CH_2−COOMe and R^3 = H).[6−10] This report focuses on the C-arylation of *N*-benzyl derivatives **4** and the formation of unsymmetrically substituted benzhydrylamines. The *N*-benzyl derivatives **4** allowed for the introduction of different substituents on the aromatic ring; thus, the effect of electron donating and electron withdrawing substituents could be fine-tuned to optimize the outcome of the arylation reaction. We used 2-Nos-amides rather than 4-Nos-amides or other derivatives because the C-arylated compounds can be readily converted to various nitrogenous heterocycles.[6−10]

Synthesis. Although all proposed synthetic steps can be performed in solution, we carried out the synthesis on solid phase. Solid-phase synthesis allows time efficient preparation of target compounds thanks to a very simple separation of synthetic intermediates bound to the solid support from soluble components of a reaction mixture by simple filtration and washing of the resin. Consequently, a high boiling reaction solvent can be advantageously used, without the need to evaporate the solvent. In addition, a high concentration of reactants in solution facilitates reaction completion.

Resin-bound *N*-benzylsulfonamides **7** (Scheme 2) were designed with an R^1 substituent with a nonactivated CH_2 group attached to the sulfonamide nitrogen; thus, arylation could only occur at the benzyl sp^3 carbon. Resin-bound amines **6** were prepared using typical solid-phase protocols (Scheme 2), well-established chemistry, and commercially available building blocks. Briefly, Wang resin[19] **5** was derivatized with 2-(Fmoc-amino)ethanol via an ether linkage by using trichloroacetimidate activation.[20] To extend the diversity of the compounds, Wang resin was also derivatized with piperazine and acylated with Fmoc-*β*Ala-OH. After removing the Fmoc group, the resin-bound amines **6** were reacted with 2-Nos-Cl. Subsequent Fukuyama alkylation[1] under Mitsunobu conditions[21,22] with a range of benzyl alcohols (Figure 2) provided the key resin-bound intermediates 7{*1*,R^2,R^3} and 7{*2*,R^2,R^3}.

In addition to substrates with single arylation sites, we prepared model compounds containing two potential arylation sites. Wang resin was esterified with 4-(Fmoc-aminomethyl)-benzoic acid. The Fmoc group was cleaved, and the resin-bound amines were derivatized with 2-Nos-Cl and subsequently alkylated with benzyl alcohols. These compounds provided sulfonamides 7{*3*,R^2,R^3} with two benzyl groups attached to the sulfonamide nitrogen and various substituents on the aromatic rings.

The resin-bound substrates **7** were exposed to a DBU solution in DMF. At room temperature, we observed C-arylation only for compounds with strong electron withdrawing groups on the aromatic ring of the benzyl group (R^3 = NO_2, CN). At an elevated temperature of 80 °C, benzhydrylamines **8** with R^3 = NO_2 (σ_p = 0.78), CF_3 (σ_p = 0.54), CN (σ_p = 0.66), and CO_2CH_3 (σ_p = 0.45) and 2- and 4-pyridyl derivatives were formed and converted to indazole oxides **9**, extending our approach to indazole oxides[6] with different substitution patterns (Table 1). No reaction was observed with compounds prepared with benzyl alcohols **8** (*p*-F σ_p = 0.06) and **9**,

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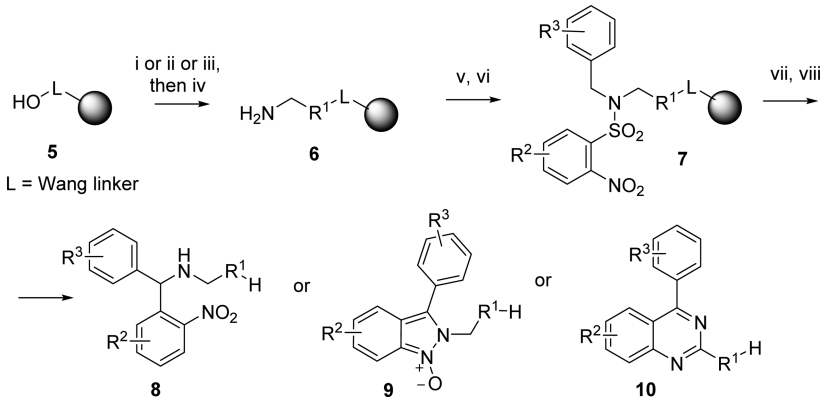
Scheme 2. Solid-Phase Synthesis[a]



[a]Reagents and conditions: (i) CCl_3CN, DBU, dichloromethane (DCM), 1 h, then Fmoc-ethanolamine, $BF_3.Et_2O$, THF, 30 min; (ii) CDI, pyridine, DCM, 2 h, then piperazine, 16 h, then Fmoc-βAla-OH, DIC, HOBt, DCM/DMF, 2 h; (iii) 4-(Fmoc-aminomethyl)benzoic acid, DIC, DMAP, DCM/DMF, on; (iv) piperidine, DMF, 15 min; (v) 2-Nos-Cl, 2,6-lutidine, DCM, 16 h; (vi) benzyl alcohols **1** − **5** or pyridylmethanols **6** and **7**, PPh_3, DIAD, THF, 2 h; (vii) DBU, DMF, for reaction temperature and time, see Table 1; (viii) 50% TFA in DCM, 1 h.

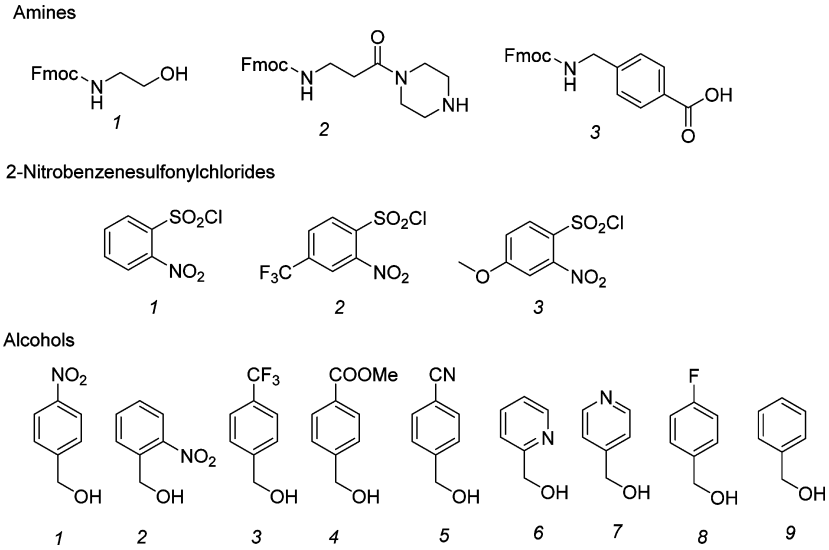


Figure 2. Structures and Numbering of the Building Blocks.

Table 1. Summary of the Synthesized Compounds 8, 9, and 10

cmpd	R^1−H	R^2	R^3	temp (°C)	time	purity[a] (%)	yield[b] (%)
8{*1,1,1*}	CH_2−OH	H	4-NO_2	rt	0.5 h	65	52
8{*2,1,5*}	CH_2−COpip	H	4-CN	rt	2 d	56[c]	72
8{*2,1,5*}	CH_2−COpip	H	4-CN	40	8 h	52	79
8{*3,1,5*}	4-$C_6H_4CO_2H$	H	4-CN	rt	2 d	55	45
9{*1,1,1*}	CH_2−OH	H	4-NO_2	rt	on	51	19
9{*1,1,2*}	CH_2−OH	H	2-NO_2	80	on	66	58
9{*1,1,3*}	CH_2−OH	H	4-CF_3	80	on	44	21
9{*1,1,4*}	CH_2−OH	H	4-CO_2CH_3	80	on	56	16
9{*1,1,5*}	CH_2−OH	H	4-CN	80	on	76	64
9{*1,1,6*}	CH_2−OH	H	2-Py	80	on	50	30
9{*1,1,7*}	CH_2−OH	H	4-Py	80	5 h	46	63
9{*1,2,5*}	CH_2−OH	4-CF_3	4-CN	rt	on	63	42
9{*1,3,5*}	CH_2−OH	4-OCH_3	4-CN	80	5 h	56	22
9{*2,1,5*}	CH_2−COpip	H	4-CN	rt	2 d	28	17
9{*2,1,5*}	CH_2−COpip	H	4-CN	40	8 h	21	21
10{*3,1,5*}	4-$C_6H_4CO_2H$	H	4-CN	80	5 h	29	51

[a]Purity of the crude products estimated from LC traces at 210−500 nm. [b]Isolated yield after HPLC purification. [c]Contained 28% of the indazole oxide.

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indicating the necessity of a strong electron-withdrawing group or heteroatom (pyridylmethanols **6** and **7**) to facilitate the DBU-mediated arylation reaction.

Next, we examined the effect of the substituent on the aromatic ring of the 2-nitrobenzenesulfonamides. The arylation and subsequent indazole oxide formation was compatible with 2-Nos-derivatives containing electron withdrawing (CF_3, compound 7{*1,2,5*}), as well as electron-donating (OCH_3, compound 7{*1,3,5*}) groups.

Regioselectivity of the DBU-mediated arylation of sulfonamides 7{*3*,R^2,R^3}, prepared using 4-aminomethylbenzoic acid, depends on the character of the R^3 substituent. In the case of compound 7{*3,1,5*} with a strong electron withdrawing group R^3 = 4-CN, the major isomer (78%) was arylated at the sp^3 benzyl carbon with the 4-CN group (CH proton singlet at 5.32 ppm and two CH_2 doublets at 3.66 and 3.58 ppm). The minor isomer (22%) was arylated at the sp^3 benzyl carbon with the 4-COOH group (CH proton singlet at 5.29 ppm and two CH_2 doublets at 3.69 and 3.64 ppm). The products were further converted to quinazolines **10** via the base-catalyzed rearrangement of 2*H*-indazole-1-oxides. The mechanism of the ring expansion of the indazole oxides to quinazolines was described in our recent publication.[10] Absence of electron withdrawing R^3 substituent (benzyl alcohols **8** and **9**) resulted in arylation of the sp^3 benzyl carbon with the 4-COOH group.

Synthesis of the indazoles and quinazolines showed that these benzhydrylamines were applicable to the synthesis of heterocycles. Further applications, previously reported on unrelated solid phase substrates, include reduction of the nitro group and subsequent reaction with an aldehyde to obtain 3,4-dihydroquinazoline derivatives.[23] The quinazolinones were prepared by cyclization with *N,N′*-disuccinimidyl carbonate,1,1′-thiocarbonyldiimidazole afforded the thio analogues.[24]

CONCLUSION

The base-mediated intramolecular arylation of benzyl sp^3 carbons by 2-Nos-amides yielded unsymmetrically substituted benzhydrylamines. The presence of electron-withdrawing substituents on the aromatic ring of the benzyl group was required for arylation. Arylation also occurred with substrates prepared from pyridylmethanols. These benzhydrylamines represent advanced intermediates for the synthesis of nitrogenous heterocycles, as demonstrated by the syntheses of indazole oxides and quinazolines. Solid-phase synthesis enables efficient combinatorial synthesis of target compounds, the entire reaction sequence was completed from commercially available building blocks in 2−3 days.

EXPERIMENTAL PROCEDURES

The solid-phase syntheses were performed in plastic reaction vessels (syringes, each equipped with a porous disc) using a manually operated synthesizer.[25] Commercially available Wang resin (100−200 mesh, 1.0 mmol/g) was used. The volume of wash solvent was 10 mL per 1 g of resin. For washing, the resin slurry was shaken with fresh solvent for at least 1 min before the solvent was changed. The yields of the crude products were calculated with respect to loading of the first building block.

Reaction with Nos-Cl. Resin **6** (1 g) was washed 3× with DCM. A solution of Nos-Cl (3 mmol) and 2,6-lutidine (3.3 mmol, 382 μL) in 10 mL of DCM was added to the resin, and the slurry was shaken at ambient temperature overnight. The resin was washed 5× with DCM.

Reaction with Alcohols (Resin 7). Resin from the previous step (250 mg) was washed 3× with anhydrous THF. A solution of benzyl alcohol (0.5 mmol) or pyridylmethanol (0.5 mmol) and triphenylphosphine (0.5 mmol, 131 mg) in 2 mL of anhydrous THF was added to the resin, and the slurry was left in a freezer (−20 °C) for 30 min. Then, a solution of DIAD (0.5 mmol, 96 μL) in 0.5 mL anhydrous THF was added, and the slurry was shaken at ambient temperature for 2 h. The resin was washed 3× with THF and 3× with DCM.

Reaction with DBU. Resin **7** (250 mg) was washed 3× with anhydrous DMF. A solution of DBU (1 mmol, 150 μL) in 2 mL of anhydrous DMF was added to the resin, and the slurry was shaken. For temperature and time, see Table 1. The resin was washed 3× with DMF and 3× with DCM.

Cleavage and Isolation (8, 9, and 10). Resin from the previous step (250 mg) was treated with 50% TFA in DCM (3 mL) for 1 h. The TFA solution was collected, and the resin was washed 3× with 3 mL of 50% TFA in DCM. The extracts were combined and evaporated under a stream of nitrogen. The oily products were dissolved in methanol (3 mL) and purified by semipreparative reverse phase HPLC.

ASSOCIATED CONTENT

Supporting Information

Analytical data for individual compounds and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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NOTE ADDED AFTER ASAP PUBLICATION

This article was published ASAP on September 12, 2014. Several compound numbers in Table 1 have been modified. The correct version was published on October 13, 2014.