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Solid-Phase Synthesis of 2-Aryl-3-alkylamino-1*H*-indoles from 2-Nitro-*N*-(2-oxo-2-arylethyl)benzenesulfonamides via Base-Mediated *C*-Arylation

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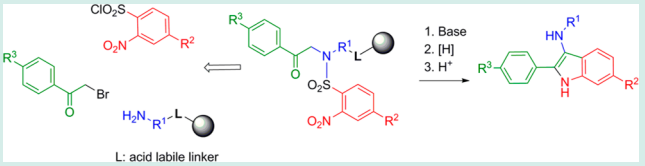
Supporting Information

ABSTRACT: Polymer-supported 2-nitro-*N*-(2-oxo-2-arylethyl)benzenesulfonamides, prepared from resin-bound amines by sulfonylation with 2-nitrobenzenesulfonyl chlorides followed by alkylation with α-bromoacetophenones, represent advanced intermediates for the synthesis of different nitrogenous heterocycles. We report their application for the synthesis of 2-aryl-3-alkylamino-1*H*-indoles via base-mediated *C*-arylation reactions followed by the reduction of the *C*-arylated intermediates. Linear precursors for *C*-arylation were prepared on solid-phase support from simple, commercially available building blocks. The effects of different substituents on the amino and aryl groups were addressed.



KEYWORDS: *solid-phase synthesis, heterocycles, indoles, C-arylation, advanced intermediates*

INTRODUCTION

2-Nitrobenzenesulfonyl chloride (2-Nos-Cl) and 4-nitrobenzenesulfonyl chloride (4-Nos-Cl) were introduced as effective protecting/activating groups for the regioselective *N*-monoalkylation of primary amines by Fukuyama et al.[1] Smooth deprotection occurs through a nucleophilic aromatic substitution mechanism via the formation of a Meisenheimer complex by treatment with a mercaptoethanol and 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) cleavage cocktail resulting in the desired secondary amine. This three-step procedure involving amine activation by Nos-Cl followed by alkylation of the activated nitrogen and then deprotection of the sulfonamide group became the general method for selective *N*-alkylation reactions in solid-phase synthesis. Initially, this method was primarily used in peptide chemistry[2,3] but was also later used in the synthesis of polyfunctional nonpeptidyl molecules; for example, this method has been used in the solid-phase synthesis of heterocycles such as the 4,7,8-trisubstituted 1,2,3,4-tetrahydrobenzo-[*e*][1,4] diazepin-5-ones (2-Nos-Cl)[4] and trisubstituted benzo-[1,4]diazepin-5-ones (4-Nos-Cl).[5]

Apart from using 2-Nos-Cl as a protecting/activating agent, it can also serve as an advantageous building block that can be effectively incorporated into the synthesis of heterocyclic compounds. 2-Nos-Cl is typically converted into the corresponding sulfonamide, and the nitro group is then reduced to an amino group, which enables the final cyclization into heterocyclic compounds derived from benzo[1,2,4]thiadiazine 1,1-dioxide, **I** and **II**[6,7] (Figure 1), or benzo[1,2,5]thiadiazepine 1,1-dioxide, **III**, **IV**, and **V**.[8−10] The synthesis of the anagrelide sulfonamide analogues (**II**) was carried out on a solid support.[6] Recently, we reported the solid-phase synthesis of benzothiadiazepines (**V**) obtained by the reduction of a sulfonamide precursor.[8]

While developing combinatorial libraries of drug-like heterocyclic compounds, our group observed an unprecedented difference in the reactivity of 2- and 4-Nos derivatives. Whereas the 4-Nos group was cleaved by treatment with the conventional cleavage cocktail of mercaptoethanol/DBU, the 2-Nos derivatives (**VI**, Figure 2) underwent intramolecular *C*-arylation followed by *N*−*N* bond formation resulting in indazole oxides, **VII**, which were also deoxygenated to the corresponding indazoles, **VIII**.[11] The 2-Nos amides (**VI**) represent advanced intermediates that can be converted into different heterocyclic compounds by modifying the substituents and selecting the appropriate reaction conditions. A further extension of the tandem *C*−*C*, *N*−*N* bond formation reactions led to more complex compounds, including pyrazino[1,2-*b*]indazol-oxides (**IX**) and their indazoles (**X**), pyrazino[1,2-*b*]indazol-oxides-1-one, **XI** (in the case of R^3 = OEt), and polycyclic heterocycles (**XII** and **XIII**). In subsequent research into the base-mediated *C*−*C* bond formation, we observed a rearrangement of the indazole oxides under mild conditions resulting in 2,3-dihydro-1*H*-imidazo[1,2-*b*]indazoles (**XIV**). The original tandem reaction was extended, when we discovered a new ring-expansion of the indazole oxides substituted with an acidic proton leading to quinazolines (**XV**;[12] and references cited therein).

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Figure 1. Nitrogenous heterocycles prepared via 2-Nos amides.

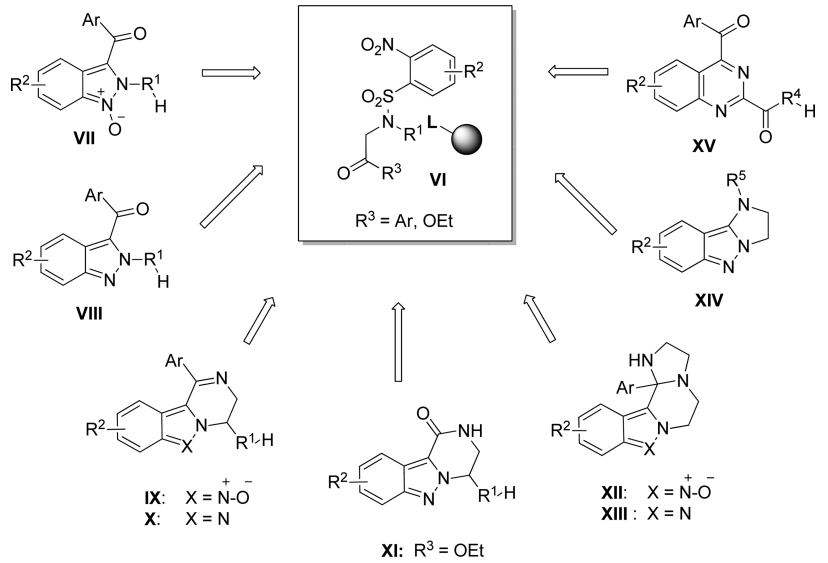

Figure 2. 2-Nos amide **VI** as an advanced intermediate leading to the various privileged structures **VII**–**XV**.

This report presents a further extension of the application of the base-labile advanced intermediate **VI**; the *C*-aryl derivative was subjected to a reduction of the nitro group[13] followed by the spontaneous cyclization to another class of heterocycles, the indoles. The term advanced intermediate refers to a substrate with two or three diversity positions that can result in the synthesis of structurally unrelated molecular scaffolds by modifying the peripheral substituents or reaction conditions.

Indole-containing molecules exhibit a remarkably wide range of biological activities, and these compounds have been referred to as privileged structures in medicinal chemistry.[14] There are many preparative methods for the solid-phase synthesis of indoles based on either ring-forming reactions (Fischer,[15] intramolecular Wittig,[16] palladium-catalyzed cyclizations,[17] and many others[18]) or linking indoles that were prepared in solution onto a solid support.[19] 2-Aryl-3-alkylamino-1*H*-indoles can be obtained using nitrilium chemistry, typically by the reaction of isocyanide with aldimines in the presence of acid.[20] Applying the conditions of the interrupted Ugi reaction, Schneekloth et al.[21] reported that electron-donating groups are required for the formation of the indole moiety. Interesting acid-triggered transformations of quinazolinones leading to 2-alkyl/aryl-1*H*-indol-3-yl-ureas have been described.[22] The authors of an international patent[23] synthesized a 3-amino-1*H*-indole moiety via the acid-assisted cyclization of phenyl-hydrazones and declared that these indole derivatives substituted at position 2 by pyrazinone were biologically active in the treatment of hyper-proliferative disorders and diseases associated with angiogenesis. Another group of 1*H*-indoles substituted with guanidine in position 3 and with an alkyl group in position 2 has been identified as a new class of antidiabetic agents.[24] Recently, gold-catalyzed solid-phase synthesis of indole derivatives was reported.[25] Resin bound nitrobenzoic acid derivatives were also reacted with alkenyl Grignard reagents as a key step of indole synthesis.[26]

To the best of our knowledge, 2-aryl-3-alkylamino-1*H*-indoles have not been prepared from 2-nitro-*N*-(2-oxo-2-arylethyl)benzenesulfonamides via base-mediated *C*-arylation. In this report, we describe an efficient and expeditious high-throughput solid-phase synthesis compatible with Merrifield[27] strategy leading to diverse 2-aryl-3-alkylamino-1*H*-indoles using amino acids, 2-Nos-Cl, and α-bromoketones as conventional building blocks.

RESULTS AND DISCUSSION

Synthesis. The syntheses were carried out on a solid-phase support. While all the synthetic steps can be performed in solution, we incorporated the specific advantages of solid-phase synthesis, particularly the expeditious preparation of the target compounds due to the very facile isolation of resin-bound intermediates from soluble components by simple filtration and washing the resin. Accordingly, any high-boiling reaction solvent can be used and subsequently removed by filtration rather than by evaporation.

Polymer-supported acyclic intermediates (**3**, Scheme 1) were prepared from diverse resin-bound amines (**1**, Figure 3). The synthesis of the acyclic precursors was carried out on Wang resin[28] and Rink amide resin[29] containing linkers suitable for an acid-mediated cleavage from the resin. Briefly, Fmoc-Ala-OH (9-fluorenylmethoxycarbonyl) and Fmoc-β-Ala-OH were attached to Wang resin using the *N*-hydroxybenzotriazole (HOBt) and *N*,*N*′-diisopropylcarbodiimide (DIC) procedure along with 4-(*N*,*N*-dimethylamino)pyridine (DMAP) as a catalyst.[30] Fmoc-4-aminobutyric acid was immobilized via the HOBt/DIC[31] peptide-coupling procedure on Rink resin. Then, Fmoc was removed to give the resin bound amines **1**{*1*–3}.

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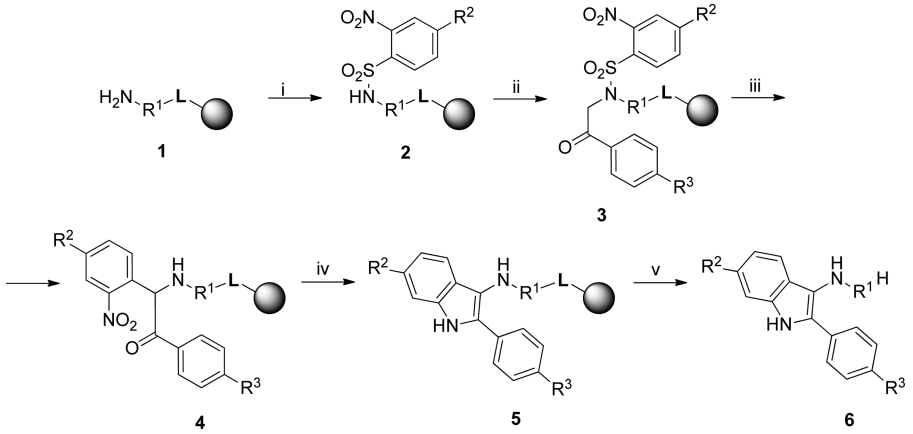
Scheme 1. Polymer-Supported Synthesis of Trisubstituted Indoles (6)[a]



[a]Reagents and conditions: (i) 2-Nos-Cl, 2,6-lutidine, DCM, rt, overnight; (ii) α-bromoacetophenone, *N*,*N*-diisopropylethylamine (DIEA), DMF, rt, overnight; (iii) base [triethylamine (TEA) or 1,4-diazabicyclo[2.2.2]octane (DABCO)], DMF, rt, 1 h or overnight (see Table 2); (iv) $Na_2S_2O_4$, K_2CO_3, tetrabutylammonium hydrogen sulfate (TBAHS), H_2O/DCM (1:1), rt, 1 h or overnight; (v) TFA/DCM (1:1), rt, 1 h or TFA/TES/DCM (5:1:4), rt, 1 h.

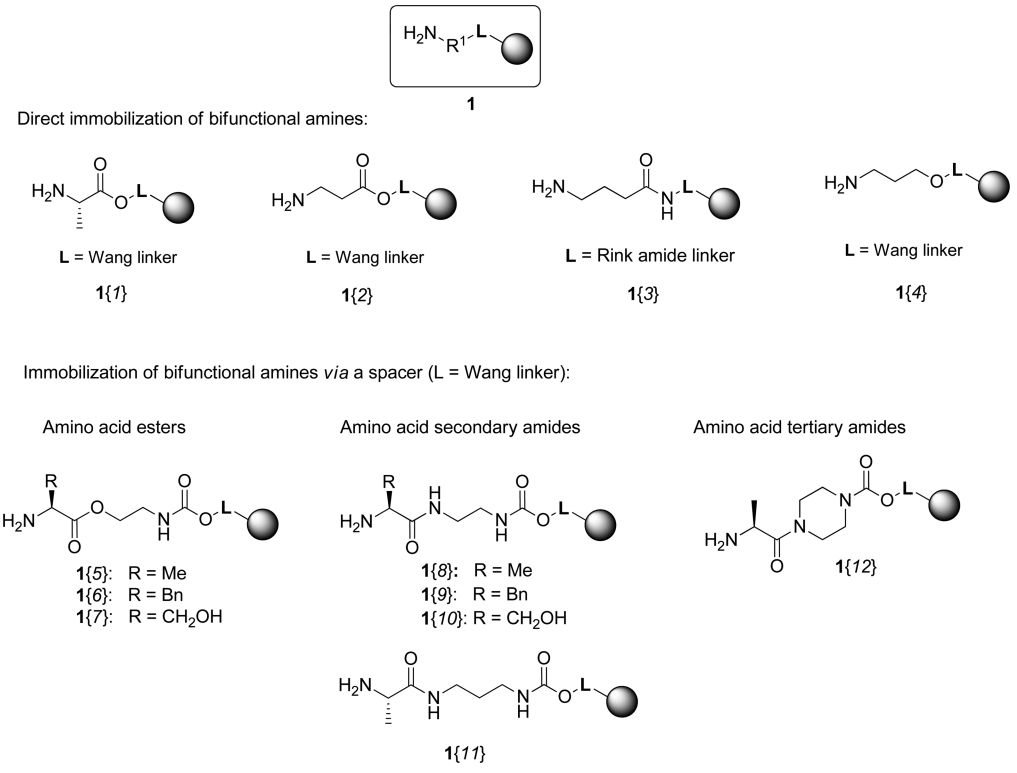


Figure 3. Structures of polymer-supported amines (**1**).

Fmoc-β-alaninol (3-aminopropan-1-ol) was attached via an ether linkage using trichloroacetimidate activation[32] followed by Fmoc cleavage, **1**{*4*}. To further increase the diversity of the resin-bound amines, 2-aminoethanol, ethylenediamine, propane-1,3-diamine, and piperazine were attached to the Wang resin via carbamate linkages using the carbonyldiimidazole (CDI) activation method[33] followed by reaction with Fmoc-protected amino acids (Ala, Phe, Ser) under the conditions of conventional peptide coupling techniques with HOBt and DIC resulting, after Fmoc deprotection, in the immobilized amino acid esters **1**{*5*}−**1**{*7*}, secondary amides **1**{*8*}−**1**{*11*} and a tertiary amide **1**{*12*} (Figure 3, **L** stands for an acid-labile linker).

A set of diverse resin-bound amines (**1**) were reacted with 2-Nos-Cl in the presence of 2,6-lutidine (Scheme 1), and the resulting sulfonamides (**2**) were alkylated with α-bromoacetophenones. The exposure of the acyclic precursors (**3**) to a base induced the *C*-arylation of methylene activated by a neighboring carbonyl group. Subsequently, the nitro group was reduced using the sodium dithionite method.[13] The target compounds (**6**) were cleaved from the resin with a cleavage cocktail of trifluoroacetic acid (TFA) in dichloromethane (DCM) with the addition of the carbocation scavenger triethylsilane (TES).[34]

Scope and Limitations. To determine the effect of substitution on the *C*-arylation and subsequent reduction to indoles,

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we prepared a set of linear precursors (**3**) with different substituents R^1, R^2, and R^3. The substituent R^1 represents the anchor to the solid support (see Figure 3). To address the effects of substituents on the aromatic rings, we prepared acyclic precursors (**3**) from 2-Nos-Cls with R^2 = H, OCH_3, and CF_3 and from bromoacetophenones with R^3 = H, OCH_3, Cl, and CH_3 (Figure 4).

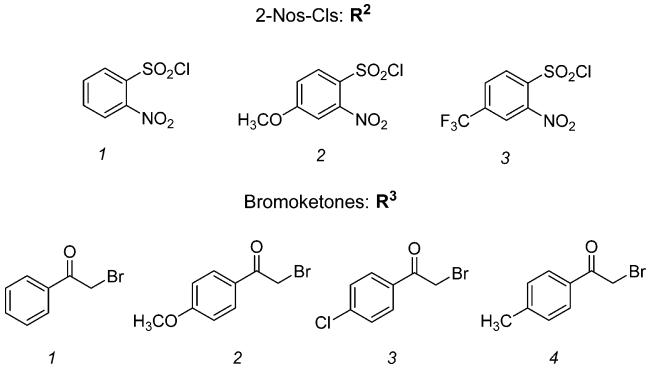


Figure 4. Structures of the building blocks: 2-Nos-Cls and bromoacetophenones.

Alkylation. The resin-bound intermediates (**3**) were prepared with all of the building blocks, although some alkylation reactions were repeated to achieve good to excellent conversions (see Table 3). In particular, this was required for compounds prepared on amino acid amides.

We observed *C*-arylation and the formation of **4** after repeated alkylation but did not observe any significant formation of indazole oxides. The *C*-arylation was triggered by DIEA present in the reaction mixture during the alkylation with bromoacetophenones. In those cases, subsequent treatment with a base was not necessary, and the next step was the reduction of the nitro group.

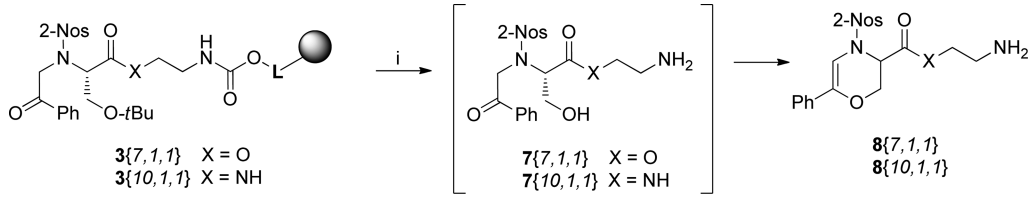
All of the resin-bound alkylated sulfonamides (**3**) afforded the expected products after cleavage from the resin, and only the Ser-derived intermediates **3**{*7,1,1*} and **3**{*10,1,1*} had indications of the formation of 3,4-dihydro-2*H*-1,4-oxazines (**8**, Scheme 2).

Arylation. The critical step of the synthesis was *C*-arylation leading to the resin-bound intermediates **4**. We have already reported that the exposure of 2-nitro-*N*-(2-oxo-2-arylethyl)-benzenesulfonamides (**3**) to DBU leads to tandem *C*−*C* bond formation followed by *N*−*N* bond formation and cyclization to indazole oxides.[11] Extended treatment with DBU resulted in ring expansion and the formation of quinazolines when the neighboring methylene group in position 2 of the indazole oxide was activated.[12] Thus, we focused on the optimization of the reaction conditions to obtain *C*-aryl derivatives (**9**), while preventing or minimizing the formation of indazole oxides (**10**) and quinazolines (**11**; Scheme 3).

To address the effect of a base, precursor **3**{*5,1,1*} was exposed to 2,6-lutidine, DABCO, DMAP, TEA, DIEA, DBU, *N,N,N′,N′*-tetramethyl-1,8-naphthalenediamine (a proton sponge), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), or 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP). The results indicated that 2,6-lutidine and DMAP were too weak to trigger *C*-arylation (see Table 1), and even after an overnight treatment, we detected the starting material **7** as the major component in the TFA-cleaved crude sample. Bases with similar structures TEA and DIEA led to *C*-aryl formation resulting in product **9** with 89% and 75% yields, respectively, after overnight treatment. An extended exposure of up to 2 days or increased temperatures up to 50 °C led to the formation of the indazole oxide **10**. The proton sponge did not provide sufficient conversion, and at 50 °C overnight, there was a mixture of **7** (55%), **9** (30%), and **10** (15%). DABCO was more reactive and gave the indazole oxide in excellent purity after overnight treatment. DBU, DBN, and BEMP all exclusively led to a quinazoline derivative, and BEMP provided the indazole oxide with the lowest crude purity. Based on these results, we tested the reactivity of all of the other sulfonamides (**3**) with TEA, DABCO, and DBU to address the effects of the substituents and to find the optimal reaction conditions for *C*-arylation.

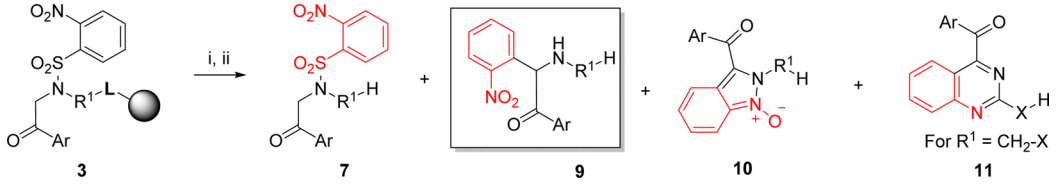
R^1 Effect. We prepared model compounds derived from amino acids attached via esters, secondary amides, and tertiary amides. A common feature of the compounds with ester linkers, **3**{*5,*R^2*,*R^3}} and **3**{*6,*R^2*,*R^3}}, was that a base was required for *C*-arylation. In contrast, the compounds with secondary amide

Scheme 2. Synthesis of the Morpholine Byproducts (8)[a]



[a]Reagents and conditions: (i) TFA/DCM (1:1), rt, 1 h.

Scheme 3. Exposure of the Advanced Intermediates 3 to a Base and Subsequent Cleavage[a]



[a]Reagents and conditions: (i) 0.1−0.5 M base, DMF or DMSO, rt to 50 °C, 5 min to 48 h (Table 1); (ii) TFA/DCM (1:1), rt, 1 h.

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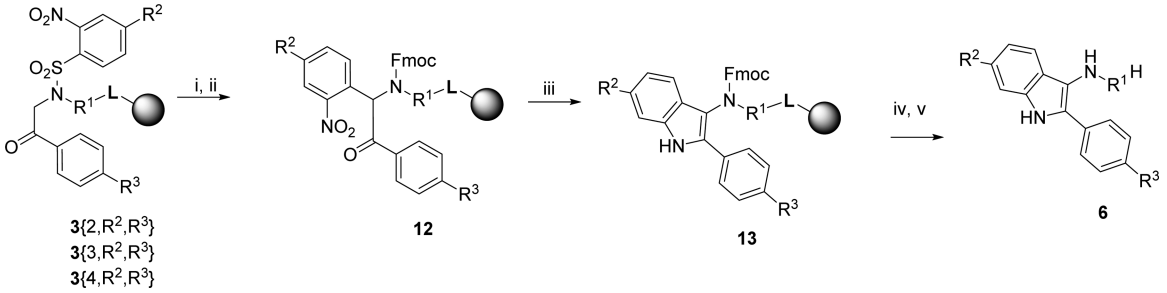
Table 1. Formation of Sulfonamides (7), *C*-Aryl Derivatives (9), Indazole Oxides (10), and Quinazolines (11) from Intermediate 3{*5,1,1*}

						relative ratio[a] [%]				
entry	base	time	conc.	solvent	temp.	**7**	**9**	**10**	**11**	impurities[b] [%]
1	2,6-lutidine	30 min	0.5 M	DMF	rt	96	4			<1
		on[c]	0.5 M	DMF	rt	91	9			<1
2	DMAP	30 min	0.5 M	DMF	rt	84	16			<1
		on	0.5 M	DMF	rt	40	33	27		<1
3	TEA	30 min	0.5 M	DMF	rt	74	26			<1
		on	0.5 M	DMF	rt	11	89			<1
		2 days	0.5 M	DMF	rt	7	92	1		<1
4	DIEA	30 min	0.5 M	DMF	rt	82	18			<1
		on	0.5 M	DMF	rt	25	75			<1
		on	0.5 M	DMF	50 °C	1	69	30		<1
5	proton sponge	30 min	0.5 M	DMF	rt	91	9			<1
		on	0.5 M	DMF	rt	70	25	5		<1
		2 days	0.5 M	DMF	rt	42	58			<1
		on	0.5 M	DMF	50 °C	55	30	15		<1
6	DABCO	30 min	0.5 M	DMF	rt	46	54			<1
		on	0.5 M	DMF	rt			100		<1
7	DBU	5 min	0.5 M	DMF	rt				100	38
		30 min	0.1 M	DMF	rt				100	45
		30 min	0.1 M	DMSO	rt				100	39
	DBN	5 min	0.5 M	DMF	rt				100	30
		5 min	0.1 M	DMSO	rt			30	70	15
		30 min	0.1 M	DMSO	rt				100	34
	BEMP	30 min	0.5 M	DMF	rt				100	51

[a]Relative ratios of compounds **7**, **9**, **10**, and **11** calculated from the LC traces at 234 nm. [b]Presence of other impurities. [c]Overnight.

Scheme 4. Fmoc Protection in the Synthesis of Indoles 6{*2−4,1,1*}[a]



[a]Reagents and conditions: (i) 0.5 M DABCO, DMF, rt, 1−4 h (see Table 3); (ii) Fmoc-Cl, DCM, rt, 40 min; (iii) $Na_2S_2O_4$, K_2CO_3, TBAHS, H_2O/DCM (1:1), rt, 1 h; (iv) piperidine, DMF (1:1), rt, 15 min; (v) TFA/TES/DCM (5:1:4), rt, 1 h.

linkers, including compounds 3{*8*,R^2,R^3}, 3{*9*,R^2,R^3}, and 3{*11*,R^2,R^3}, already contained 40−80% of the *C*-arylated structure (**4**) after reaction with *α*-bromoacetophenone. Therefore, we did not expose the resin-bound alkylated compounds to other bases because the basic conditions of the alkylation reaction step (DIEA) were sufficient. The only exception was Ser 3{*10,1,1*}; a short treatment with a base was necessary to induce the *C*-arylation of this compound. The amino acid tertiary amides 3{*12*,R^2,R^3} and 3{*13*,R^2,R^3} required a short treatment with a base for *C*-arylation.

The resin-bound intermediates (**3**) prepared using Fmoc-amino acids and 3-(Fmoc-amino)-1-propanol (resins **1**{*1−4*}) afforded the alkylated sulfonamides 3{*1−4,1,1*} with very high purities (95%), and no *C*-arylated side-products were detected. However, treatment with a base resulted in rapid *C*-arylation and the subsequent spontaneous formation of indazole oxides (when using TEA or DABCO) or, in the case of the Ala derivative, quinazolines (when using DBU). Optimization of the reaction conditions (different bases, solvents, and temperatures) did not provide the *C*-arylated compound with a satisfactory purity, and only 32% of the *C*-arylated intermediate **9**{*1,1,1*} was observed with 3{*1,1,1*} when using 0.5 M TEA overnight. To avoid the formation of indazole oxides, we protected the secondary amino group with an Fmoc group (Scheme 4), reduced the nitro group, and subsequently cleaved the protecting Fmoc group to yield the desired indoles (**6**).

Effect of R^2 and R^3. The synthesis was compatible with both electron withdrawing and electron donating substituents present on either aromatic ring. Electron withdrawing groups accelerated not only the *C*-arylation but also the subsequent undesirable cyclization to indazole oxides. An electron donating group (OCH_3) increased the stability of the sulfonamides, and the rearrangement leading to *C*-arylation required several days.

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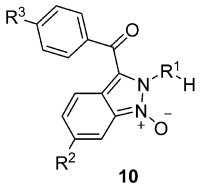
Stability of 4. The resin-bound intermediates (**4**) were analyzed after exposure to a base and also after 2 weeks of storage in a refrigerator at 5 °C. Although the resin was washed very thoroughly to remove any residual base, we observed a significant amount of spontaneous indazole oxide formation upon extended storage. Therefore, we carried out the reduction of the *C*-aryl derivatives without delay to prevent spontaneous cyclization to indazole oxides.

Reduction. In the subsequent step, the nitro groups of the resin-bound intermediates (**4**) were reduced using a sodium dithionite method developed for solid-phase synthesis.[13] The effect of the reaction time was addressed by the LC/MS analysis of samples cleaved from the resin (Table 2). An overnight reduction of the amino acid ester-containing compounds **4**{*5*,R^2,R^3} and **4**{*6*,R^2,R^3} provided respectable purities of the target indoles (71−90%). However, we observed an increasing amount of a compound formed by the reduction of the ketone to an alcohol (10−29%). Similar results were observed with the secondary amide-derived compounds **4**{*8*,R^2,R^3} and **4**{*10*,R^2,R^3}. A 1 h reduction eliminated the formation of the alcohol. In the case of the tertiary amide **4**{*12*,R^2,R^3}, even a long reduction time did not lead to a reduction to alcohol, and the amine underwent cyclization to indole.

It is worth mentioning that the indazole oxide present in the resin-bound intermediates was reduced to indazole, offering a convenient method for the reduction of indazole oxides to indazoles on a solid-phase support (Scheme 5). To confirm the structures of the side-products, compounds **16**{*1,1,1*} and **16**{*8,3,1*} were isolated and purified, and the structures were confirmed by NMR spectroscopy.

Table 2. Side-Product Formation from Intermediate 4



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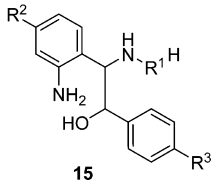


15

		indazole oxide **10**[a]		alcohol **15**[b]	
entry	resin	after reaction	stored 14 d	1 h	on
1	4{*5,1,1*}	11%	NT	3%	25%
2	4{*5,1,3*}	7%	12%	11%	29%
3	4{*6,1,1*}	<1%	NT	10%	14%
4	4{*8,1,1*}	<1%	28%	<1%	50%
5	4{*8,1,2*}	29%	30%	<1%	19%
6	4{*8,1,3*}	5%	NT	<1%	27%
7	4{*8,1,4*}	<1%	NT	<1%	31%

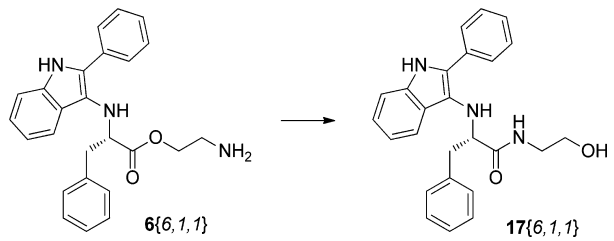
[a]Relative amount of the indazole oxide **10** after reaction with a base and after storage at 5 °C for 14 days. [b]Relative amount of the alcohol **15** after reduction for 1 h and overnight (on); NT, not tested.

Cleavage. The last step of the synthesis was the cleavage of the target compounds (**6**) from the resin with the cleavage cocktail of a TFA solution in DCM with the addition of the carbocation scavenger triethylsilane (TES) if appropriate.[34] Indoles are known to be sensitive to acids. The LC/MS analysis indicated a partial decomposition of the indoles after prolonged treatment with TFA/DCM (1:1). To reduce the potential alkylation of the indoles during acid-mediated cleavage, we evaluated the effects of scavengers in cleavage cocktails of 95% TFA in H_2O and 10% TES in TFA/DCM. The best results were provided by the addition of TES, and the LC/MS analysis of the cleaved solution did not show any signs of deterioration after 2 h.

Purification. Crude indoles were purified by semipreparative reversed-phase HPLC using the mobile phases of aqueous ammonium acetate buffer and acetonitrile. A few target compounds were purified using aqueous 0.1% TFA/acetonitrile (see the Supporting Information) because of the improved separation with an acidic mobile phase. Table 3 summarizes the synthesized 2-aryl-3-alkylamino-1*H*-indoles with three positions of diversification that were positioned at the amino group (R^1), the fused aromatic ring (R^2), and the aromatic ring in position 2 of the indole (R^3). The indoles containing basic amino groups for the R^1 substituent were isolated in the form of acetates or trifluoroacetates. All the compounds were characterized by ^1H and ^{13}C NMR spectroscopy and LC/MS analysis. The compositions of selected compounds were also confirmed by HRMS.

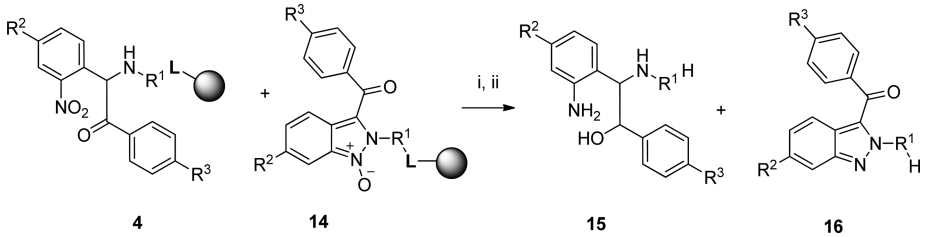
It is important to mention that the ester-based indoles **6**{*5*,R^2,R^3} and **6**{*6*,R^2,R^3} purified in the ammonium acetate buffer underwent an O−N shift upon storage at ambient temperature for an extended period of time.[8] To confirm the formation of an amide, we isolated compound **17** formed from ester **6**{*6,1,1*} and characterized the amide (Scheme 6). Purification in aqueous 0.1% TFA prevented the O−N shift.

Scheme 6. O−N Shift of the Ester-Based Derivative (6)



6{*6,1,1*} **17**{*6,1,1*}

Scheme 5. Side Products of Reduction: Alcohol Derivative (15) and Indazole (16)[a]



4 **14** **15** **16**

[a]Reagents and conditions: (i) $Na_2S_2O_4$, K_2CO_3, TBAHS, H_2O/DCM (1:1), rt, overnight; (ii) TFA/DCM (1:1), rt, 1 h.

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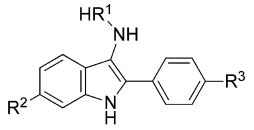
Table 3. Synthesized Derivatives of 2-Aryl-3-amino-1*H*-indoles (6)



6{R^1,R^2,R^3}

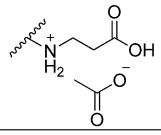
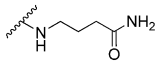
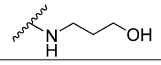
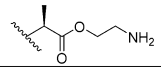
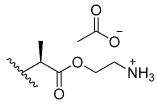
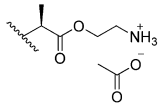
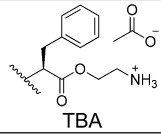
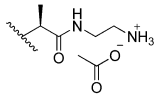
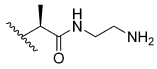
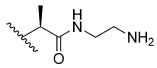
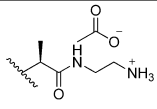
Entry	Cmpd	R^1-H	R^2	R^3	*C*-aryl.[a]	Purity of **6**[b]	Yield[c]
1	**6**{*2,1,1*}		H	H	DABCO/ 1 h	50%	37
2	**6**{*3,1,1*}		H	H	DABCO/ 4 h	46%	9
3	**6**{*4,1,1*}		H	H	DABCO/ 2 h	52%	37
Esters							
4	**6**{*5,1,1*}		H	H	TEA/on	60%	32
5	**6**{*5,1,2*}		H	OCH_3	TEA/72 h	80%	27
6	**6**{*5,1,3*}		H	Cl	TEA/4 h	50%	15
7	**6**{*6,1,1*}	 TBA	H	H	TEA/6 h	45%	13
Amides							
8	**6**{*8,1,1*}		H	H	NN, 2x alkyl.	40%	11
9	**6**{*8,1,2*}		H	OCH_3	NN, 2x alkyl.	48%	39
10	**6**{*8,1,3*}		H	Cl	NN, 1x alkyl.	55%	19
11	**6**{*8,1,4*}		H	CH_3	NN, 2x alkyl.	60%	13

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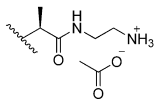
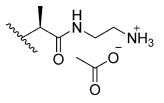
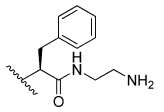
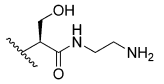
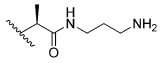
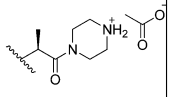
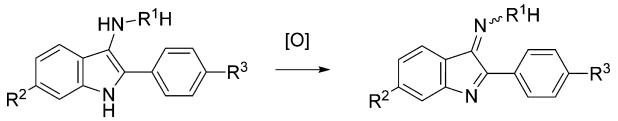
Table 3. continued

12	6{8,2,1}		OCH_3	H	DABCO/ 7 h	48%	18
13	6{8,3,1}		CF_3	H	NN, 1x alkyl.	50%	55
14	6{9,1,1}		H	H	NN, 3x alkyl.	57%	35
15	6{10,1,1}		H	H	DABCO/ 30 min	80%	49
16	6{11,1,1}		H	H	NN, 3x alkyl.	50%	18
17	6{12,1,1}		H	H	DABCO/ 3 h	55%	34

[a]C-arylation conditions: 0.5 M base/time; NN = not necessary, after reaction with bromoacetophenone there was sufficient conversion to the C-arylated structure. [b]Purity of crude indole estimated from the LC traces. [c]Yield (%) after HPLC purification based on the initial loading of the resin.

Scheme 7. Air Oxidation of Indoles (6) to *N*-Alkyl-2-aryl-3*H*-indol-3-imines (18)



6 18

As an endnote, the purities of the 3-alkylaminoindoles deteriorated upon long-term storage at ambient temperature. The LC/MS analysis indicated the formation of a product formed by air oxidation, and the molecular ions corresponded to *N*-alkyl-2-aryl-3*H*-indol-3-imines (**18**, Scheme 7). The products of air oxidation were not isolated; the composition of these compounds was verified by HRMS analysis (see the Supporting Information). Analogous oxidations have previously been reported.[35,36]

CONCLUSION

We describe an efficient route for the solid-phase synthesis of 2-aryl-3-alkylamino-1*H*-indoles from 2-nitro-*N*-(2-oxo-2-arylethyl)benzenesulfonamide acyclic precursors via base-mediated *C*-arylation followed by the reduction of the nitro group and spontaneous cyclization. The synthesis proceeded under mild conditions and used commercially available building blocks: Fmoc protected amino acids, 2-nitrobenzenesulfonyl chlorides, and bromoacetophenones. The synthesis encompassed three diversification positions and tolerated a broad range of substituents.

EXPERIMENTAL PROCEDURES

The solid-phase syntheses were carried out in plastic reaction vessels (syringes, each equipped with a porous disc). The volume of the 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. All of the reactions were carried out at ambient temperature unless otherwise stated. Commercially available (Advanced ChemTech, Louisville KY) Rink resin (100−200 mesh, 0.66 mmol/g) and Wang resin (100−200 mesh, 1.0 mmol/g) were used. The yields of the crude products were calculated with respect to the loading of the first building block. The reaction conditions for the individual steps of the syntheses were analogous to those reported in our previous communications.[8,11,13,37]

Reaction with Nos-Cl (resin 2). Resin **1** (1 g) was washed three times 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 five times with DCM.

Alkylation with Bromoacetophenone (resin 3). Resin **2** (1 g) was washed three times with DCM and then three times with DMF. A solution of 0.5 M bromoacetophenone (5 mmol) and 0.5 M DIEA (5 mmo, 870 μL) in 10 mL of DMF was added, and the syringe was shaken at ambient temperature overnight. The resin was washed five times with DMF and three times with DCM. If the conversion to resin **3** was not complete, the reaction with bromoacetophenone was repeated.

Reaction with a Base (resin 4). Resin **3** (250 mg) was washed three times with DCM and then three times with DMF. A solution of

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0.5 M base (350 μL of TEA or 280 mg of DABCO, see Table 3) in 5 mL of DMF was added, and the resin slurry was shaken at ambient temperature for 1−72 h (see Table 3). Resin was washed three times with DMF and three times with DCM.

Reduction of Nitro Group (Resin 5). Resin **4** (250 mg) was washed three times with DCM. A solution of $Na_2S_2O_4$ (525 mg, 3 mmol), K_2CO_3 (480 mg, 3.5 mmol), and TBAHS (85 mg, 0.25 mmol) in H_2O/DCM (50%, 5 mL) was then added to the resin, and the slurry was shaken at ambient temperature for 1 h. The resin was washed three times with H_2O/DCM (50%), three times with MeOH/DCM (50%), and three times with DCM.

Cleavage and Isolation (6). Resin **5** (250 mg) was treated with 50% TFA in DCM (3 mL) for 1 h. The TFA solution was collected, and the resin was washed three times 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 associated with this article. 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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