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3-Alkyl-3-(alkylamino)indolin-2-ones via Base-Mediated C-Arylation of 2-Nitrobenzenesulfonamides

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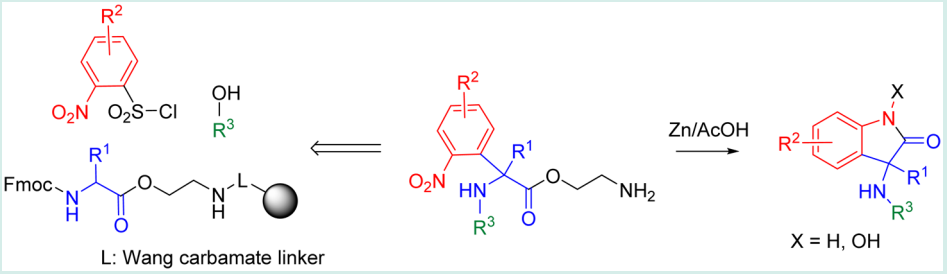
Supporting Information



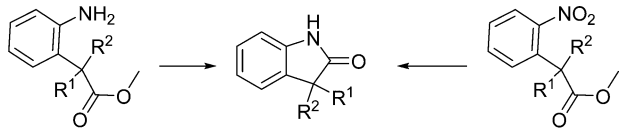
ABSTRACT: Resin-bound intermediates prepared from polymer-supported amino acid esters, 2-nitrobenezenesulfonyl chlorides, and alcohols were used to synthesize 3-alkyl-3-(alkylamino) indolin-2-ones. The key step of the reaction sequence was the formation of a quaternary carbon via the base-mediated C-arylation of 2-nitrobenzenesulfonamides. The cleavage of the acyclic precursors from the resin and subsequent reduction of the nitro group by Zn in acetic acid triggered the spontaneous cyclization of the arylated compounds to indolinones. The synthesis was carried out using simple commercially available building blocks under mild conditions and provided the 3,3-disubstituted indolinone derivatives with good overall yields however, the arylation reaction resulted in the epimerization of the quaternary carbon.

KEYWORDS: *arylation, solid-phase synthesis, C−C bond formation, nitrobenzenesulfonamides, heterocycle, quaternary carbon, oxindole*

The 3,3′-disubstituted indolin-2-one (oxindole) is a privileged heterocyclic motif that forms the core of a large family of alkaloid natural products with relevant bioactivity profiles. The tetrasubstituted carbon contained in the heterocyclic compounds provides interesting structural properties in the development of related compounds, such as potential medicinal agents or biological probes. Biological activity of 3-amino-2-oxindoles against a variety of targets were reported, including anxiety and depression (SSR149415)[1] and as antimalarial agents (NITD609).[2] Particularly spirooxindoles have recently attracted attention as potential anticancer agents[3,4] including the first PLK4 inhibitor that has entered phase I clinical trials for the treatment of solid tumors.[5]

Not surprisingly, oxindole has attracted immense interest from synthetic chemists as a prominent privileged structure.[6] The most frequently used synthetic route to oxindoles **1** involves lactam formation from derivatives of 2-(2-aminophenyl)acetate **2** (Scheme 1), reported for the first time in 1961.[7] This method has been used countless times with a variety of substitution patterns, often using the nitro derivatives **3** that provide target compounds spontaneously upon nitro group reduction (for a review see ref 8). However, the synthesis of 3-alkyl-3-(amino)indolin-2-ones (**1**, $R^1 = NH_2$) from 2-amino-2-(2-aminophenyl)acetates has been reported only once.[9] The key intermediate **3** ($R^2 = NH_2$) was prepared by arylation of benzylidene-protected amino acid ester with 2-fluoronitrobenzene. Synthetic route to access *N*-alkyl derivatives (**1**, $R^1 = NH\text{-}R^3$) using the lactam-forming route has not been reported.

Scheme 1. Synthesis of 2-Oxindoles 1 via Lactam Formation



2 **1** **3**

Alternative ring closing chemistries based on intramolecular arylation of acyclic intermediates has provided routes to *N*-alkyl derivatives **4** (Scheme 2). Several laboratories described cyclization of 2-bromoanilines acylated with amino acids (**5**) using Pd-catalyzed enolate arylation in the presence of NaO*t*-

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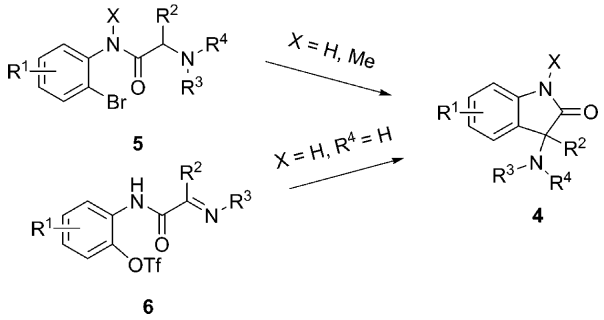
Scheme 2. Synthesis of 3-Amino-2-oxindoles via Intramolecular Arylation



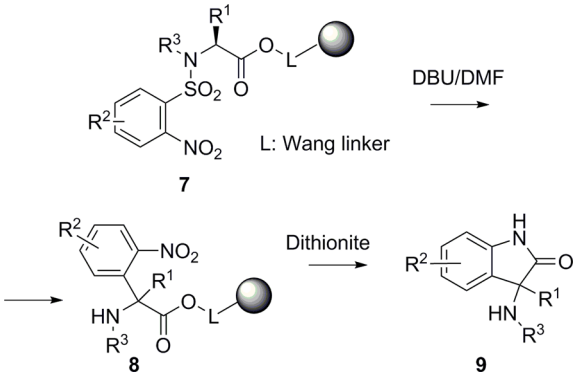
Bu,[10,11] or KO*t*-Bu without a catalyst.[12] Pd-catalyzed asymmetric intramolecular arylation in the presence of chiral *N*-heterocyclic carbene ligand provided products with up to 97% *ee*.[13] Recently, the synthesis of enantiomerically enriched 3-amino-2-oxindoles through the palladium-catalyzed asymmetric intramolecular arylation of ketimines **6** was reported.[14]

While 2-oxindole derivatives were prepared via the intramolecular Heck reaction on Rink amide resin,[15] the solid-phase synthesis of 3-alkyl-3-(alkylamino)indolin-2-ones has not been reported. We recently described the solid-phase synthesis of 2-alkyl-2-((*N*-(benzyl)-2-nitrophenyl) sulfonamide) acetic acid esters and amides through base-mediated intramolecular arylation.[16,17] These acyclic intermediates with three points of diversification are referred to as advanced intermediates and can be used to synthesize diverse heterocycles. In this contribution, we report the solid-phase synthesis of 3-alkyl-3-(alkylamino)-indolin-2-ones.

Synthetic steps were carried out on a solid support because of specific advantages that allowed the time-efficient preparation of target compounds. The soluble components of the reaction mixture are separated very easily from a resin-bound intermediate through 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 reactant concentration in the solution facilitates completion of the reaction.

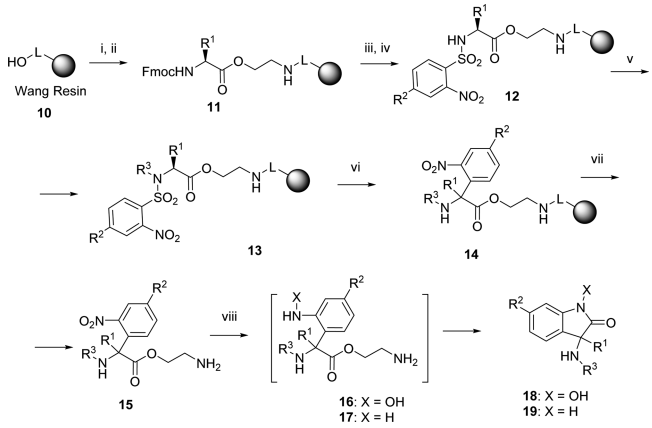
The N-alkylated 2-nitrobenzenesulfonamides (Nos amides) of the resin-bound amino acid esters **7** contain an acidic proton on the α-carbon and represent generic structures of 2-Nos amides amenable to base-mediated intramolecular C-arylation.[18−22] These compounds yielded resins **8** (Scheme 3). The quaternary carbon-containing secondary amines **8** are suitable

Scheme 3. Proof of Concept



intermediates for synthesizing indolinones **9**: the reduction of the nitro group triggered spontaneous cyclization with concurrent release of the product **9** from the resin. Although this reaction sequence provided the target compounds under mild conditions, it required that the products be isolated from the reaction mixture, which contained a reducing agent (typically tin(II) chloride[23] or sodium dithionite and PTC[24]). Therefore, we modified the synthesis scheme to be more practical. We included an ethanolamine linker between the Wang resin and the amino acid (Scheme 4). This modification

Scheme 4. Solid-Phase Synthesis of 3-Alkyl-3-(alkylamino)indolin-2-ones[a]



[a]Reagents and conditions: (i) CDI, pyridine, DCM, rt, 2 h, then ethanolamine, rt, 16 h; (ii) Fmoc-amino acid, HOBt, DIC, DMAP, DCM/DMF 1:1, rt, 16 h; (iii) piperidine, DMF, rt, 15 min; (iv) 2-Nos-Cl's, 2,6-lutidine, DCM, rt, on; (v) alcohols, PPh_3, DIAD, THF, rt, on; (vi) DBU, anhydrous DMF, rt, on; (vii) TFA/DCM 1:1, rt, 2 h; (viii) Zn/AcOH, rt, 2 h (for compounds **18**), 80 °C, on (for compounds **19**).

allowed the nitro derivative to be cleaved from the resin as an ester and enabled the subsequent reduction followed by spontaneous cyclization by Zn in acetic acid. After the reduction in the acetic acid solution was complete, the solution was filtered, diluted with water and purified by HPLC.

The Wang resin[25] **10** was derivatized with ethanolamine via a carbamate linkage[26] using the carbonyldiimidazole (CDI) activation method.[27] Esterification with Fmoc-protected amino acids was carried out under conventional conditions using *N*-hydroxybenzotriazole (HOBt) and *N*,*N*′-diisopropylcarbodiimide (DIC) catalyzed with 4-(*N*,*N*-dimethylamino)-pyridine (DMAP). The Fmoc was then removed from resin **11**, and the resin-bound amino acid esters were reacted with 2-Nos-Cl units to yield resin **12**. The 2-Nos protecting/activating group facilitated a Fukuyama alkylation[28,29] on the activated nitrogen. The Fukuyama alkylation was carried out under Mitsunobu conditions using a range of alcohols containing diverse functionalities, including alkanes, alkenes, aromatic ring and ethers (Figure 1). The exposure of resin **13** to 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in anhydrous DMF triggered the C-arylation and yielded **14**. The reaction outcome was monitored by the LCMS analysis of a sample released from the resin using a cleavage cocktail composed of 50% TFA in dichloromethane (DCM) to afford the acyclic intermediate **15**. Finally, the cleaved compounds **15** were dissolved in AcOH and a zinc reduction of the nitro group yielded *N*-hydroxyaniline **16** and/or the aniline derivative **17**, which spontaneously

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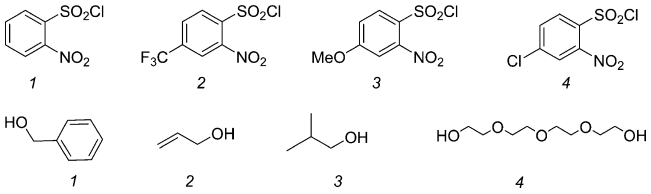

Figure 1. Structures of building blocks: 2-Nos chlorides and alcohols.

cyclized and afforded 3-alkyl-3-(alkylamino) indolin-2-ones **18** and **19** (Table 1).

Table 1. Synthesized *N*-Hydroxyindolinones 18 and Indolinones 19

entry	compound	NH–CH(R^1)–CO	R^2	R^3	purity[a] [%]	yield[b] [%]
1	**18**{*1,1,1*}	Ala	H	Bn	85	31
2	**18**{*1,1,2*}	Ala	H	allyl	75	55
3	**18**{*1,1,3*}	Ala	H	*i*-But	44	59
4	**18**{*1,1,4*}	Ala	H	$(EG)_4$	49	52
5	**19**{*1,1,1*}	Ala	H	Bn	52	72
6	**19**{*1,1,2*}	Ala	H	allyl	82	82
7	**19**{*1,1,3*}	Ala	H	*i*-But	57	45
8	**19**{*1,1,4*}	Ala	H	$(EG)_4$	35	22
9	**19**{*1,2,1*}	Ala	CF_3	Bn	99	33
10	**19**{*1,2,2*}	Ala	CF_3	allyl	65	34
11	**19**{*1,3,1*}	Ala	OMe	Bn	99	27
12	**19**{*1,3,2*}	Ala	OMe	allyl	75	31
13	**19**{*1,4,1*}	Ala	Cl	Bn	99	38
14	**19**{*1,4,2*}	Ala	Cl	allyl	99	35
15	**19**{*2,1,2*}	L-Ala + D-Ala	H	allyl	99	79
16	**19**{*3,1,1*}	D-Ala	H	Bn	99	76
17	**19**{*3,1,2*}	D-Ala	H	allyl	84	68
18	**19**{*4,1,1*}	Phe	H	Bn	94	63
19	**19**{*4,1,2*}	Phe	H	allyl	99	44
20	**19**{*5,1,1*}	Val	H	Bn	93	37
21	**19**{*5,1,2*}	Val	H	allyl	84	62

[a]Purity of the crude product. [b]Yields of HPLC-purified compounds **18** and **19** after a 7-step synthesis.

To address the scope and limitations of this synthetic route, we prepared compounds using a set of three types of building blocks: four amino acids (L-Ala, D-Ala, L-Phe, and L-Val), four 2-Nos chlorides (2-NO_2, 2,4-diNO_2, 2-NO_2-4-Cl, and 2-NO_2-4-CF_3) and four alcohols (benzyl alcohol, allyl alcohol, *i*-butyl alcohol, and tetraethylene glycol). A reduction performed at room temperature (rt) for 2 h afforded a mixture of *N*-hydroxyindolinones **18** (yield 31–59%) and indolinones **19**. To facilitate a complete reduction, indolinones **19** were prepared at 80 °C overnight (on), yielding mostly highly pure crude products (yields 22–82%). The results are summarized in Table 1.

The synthetic sequence provided the expected indolinones with all of the tested amino acids, and the Ala-derived compounds yielded marginally purer crude products. Next, we examined the effect of the substituent on the aromatic ring of the 2-Nos amides. The arylation and subsequent indolone formation were compatible with the 2-Nos-derivatives containing electron-withdrawing (CF_3, **19**{*1,2,1*} and **19**{*1,2,2*}), as well as electron-donating (OCH_3, compound **19**{*1,3,1*} and **19**{*1,3,2*}) groups. The compounds prepared with R^2 = 2,4-diNO_2 decomposed immediately after the addition of Zn. Finally, all of the tested alcohols yielded higher product yields when benzyl alcohol was used as R^1 instead of allyl alcohol.

Chiral HPLC Analysis. Because the C-arylation occurred on an asymmetric carbon, we examined the optical purity of the products using a chiral HPLC column. The results of the analytical chiral separation indicated the almost-complete epimerization of the quaternary carbon. A search for a chiral base to trigger an enantioselective C-arylation is underway.

We have reported an efficient solid-phase synthesis of 3-alkyl-3-(alkylamino) indolin-2-ones from 2-Nos sulfonamide via a base-mediated C-arylation followed by the reduction of the nitro group using zinc in acetic acid and by spontaneous cyclization. The synthesis proceeded under mild conditions and involved the use of commercially available building blocks: Fmoc-protected amino acids, 2-nitrobenzenesulfonyl chlorides and alcohol derivatives. The synthesis encompassed three diversification positions and tolerated a range of various substituents; however, the C-arylation resulted in the almost-complete epimerization of the quaternary carbon.

■ EXPERIMENTAL PROCEDURES

The solid-phase syntheses were performed in plastic reaction vessels (syringes equipped with one porous disc each) using a manually operated synthesizer. 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. Commercially available Wang resin (100–200 mesh, 1.0 mmol/g) was used. The yields of the crude products were calculated with respect to the loading of the first building block.

Reaction of the Wang Resin with Ethanolamine. The Wang resin (1 g) was swollen in DCM and washed 3× with DCM. A solution of CDI (5 mmol, 811 mg) and pyridine (5 mmol, 404 μL) in 10 mL of DCM was added to the resin slurry and shaken at rt for 3 h. The resin was washed 3× with DCM. The product was immediately used for the next step. The resin was swollen in DCM. A solution of ethanolamine (5 mmol, 315 μL) in 10 mL of DCM was added to the resin slurry and shaken at rt overnight. The resin was washed 3× with DCM.

Esterification with Fmoc-Protected Amino Acids (Resins 11). Ethanolamine resin (1 g) was swollen in DCM (3×), and Fmoc-amino acid (2 mmol), HOBt (2 mmol, 306 mg), DMAP (0.2 mmol), and DIC (2 mmol, 309 μL) in 10 mL of DCM/DMF (1:1) were added. The resin was shaken at rt overnight and washed 3× with DMF and 3× with DCM.

Reaction with Nos-Cl (Resin 12). Resin **11** (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 13). Resins **12** (250 mg) were washed 3× with anhydrous THF. A solution of alcohol (0.5 mmol) and triphenylphosphine (0.5 mmol, 131 mg) in 2 mL of anhydrous THF was added to the resin, and the resulting mixture was subsequently left in a freezer for 30 min. A solution of DIAD (0.5 mmol, 96 μL) was then added, and the resulting slurry was shaken at rt overnight. The resin was washed 3× with THF and 3× with DCM.

Reaction with DBU (Resin 14). Resin **13** (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 overnight at ambient temperature. The resin was washed 3× with DMF and 3× with DCM.

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Cleavage (Compounds 15). Resin **14** was treated with 50% TFA in DCM for 2 h. The TFA solution was collected, the resin was washed 3× with 50% TFA in DCM, and the extracts were combined and evaporated by a stream of nitrogen to give oily products.

Reduction and Isolation (Compounds 18 and 19). The oily compounds **15** were dissolved in acetic acid (3 mL), powdered zinc (2 g) was added, and the reaction mixture stirred at room temperature for 2 h to obtain *N*-hydroxyindolinones **18** and at 80 °C overnight to facilitate the formation of indolinones **19**. The solution was filtered, diluted with water and purified by semipreparative reverse-phase HPLC. Alternatively, the compounds were dried by a stream of nitrogen, dissolved in methanol and purified by HPLC.

■ ASSOCIATED CONTENT

Supporting Information

Analytical data for individual compounds and NMR spectra associated with this article. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscombsci.5b00068.

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Notes

The authors declare no competing financial interest.

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