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Base-Mediated Intramolecular C- and N-Arylation of N,N-Disubstituted 2-Nitrobenzenesulfonamides: Advanced Intermediates for the Synthesis of Diverse Nitrogenous Heterocycles

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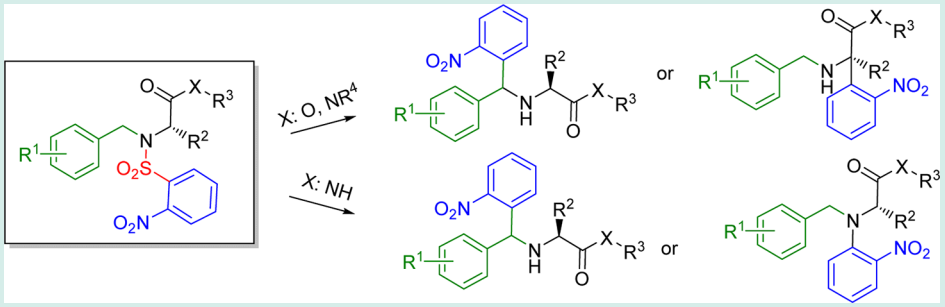
Supporting Information



ABSTRACT: Structural and electronic features that facilitate and direct the intramolecular C- and N-arylation of 2-alkyl-2-{[*N*-(benzyl)-2-nitrophenyl]sulfonamido}acetic acid esters and amides were examined. The substitution pattern and amino acid carboxy-terminal functionality determined the arylation position. C/N-arylated products represent advanced intermediates for combinatorial synthesis of diverse nitrogenous heterocycles, including indazoles, quinazolinones, quinoxalinones, and 3-amino-2-oxindoles.

KEYWORDS: *arylation, nitrobenzenesulfonamides, C−C bond formation, heterocycle, diversity-oriented synthesis*

INTRODUCTION

The development of efficient syntheses of diverse heterocyclic compounds from common precursors by changing the reaction conditions or substitution pattern of precursors is a very practical and valuable undertaking. Diversity-oriented synthesis,[1] which produces structurally unrelated molecular scaffolds through one synthetic route and takes advantage of solid-phase synthesis, has attracted the interest of numerous laboratories around the world.[2] In this report, we present our contributions to the development of advanced intermediates for the synthesis of structurally unrelated compounds. 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.

Fukuyama alkylation of 2- or 4-nitrobenzenesulfonylamides (Nos amides) is recognized as a versatile and efficient route for the synthesis of secondary amines.[3,4] The introduction of the Nos protecting/activating group via Nos-Cl is straightforward, and alkylation can be achieved with electrophiles or alcohols. Removal of the Nos group from secondary amines with sulfur nucleophiles is also straightforward. Solid-phase synthesis particularly benefits from this reaction sequence because all three steps proceed with excellent conversion and because the isolation of resin-bound intermediates takes only minutes.[5−7] However, in addition to serving as a protecting/activating group, the Nos group can be utilized to form diverse nitrogenous heterocycles.

We previously reported the solid-phase synthesis of 2*H*-indazole 1-oxides (Scheme 1) via tandem carbon−carbon bond formation followed by nitrogen−nitrogen bond formation.[8,9] The key transformation involved C-arylation triggered by a DBU-mediated Smiles-type rearrangement of 2-Nos amides. This very efficient (high yield and purity were obtained using commercially available building blocks) synthesis of indazoles prompted us to expand the chemical route and apply C-arylation to the synthesis of indazole-derived heterocycles, including pyrazino[1,2-*b*]indazoles[9] and 2-(2-amino/hydroxyethyl)-1-aryl-3,4-dihydropyrazino[1,2-*b*]indazole-2-iums, which cyclized to fused tetracyclic heterocycles[10] and rearranged to 2,3-dihydro-1*H*-imidazo[1,2-*b*]indazoles.[11] Base-

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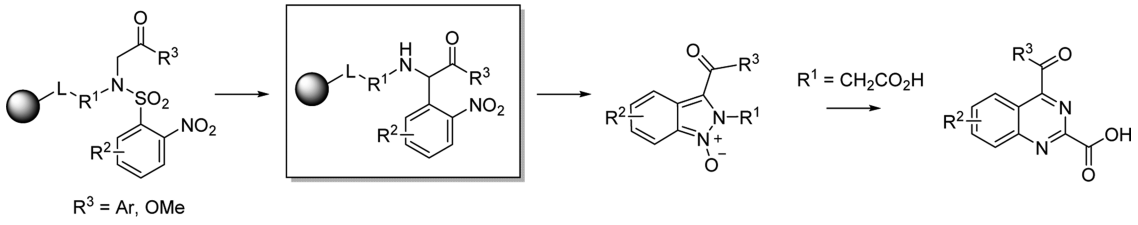
Scheme 1. Reported Syntheses of Heterocycles from 2-Nitrobenzenesulfonamides via C-Arylation



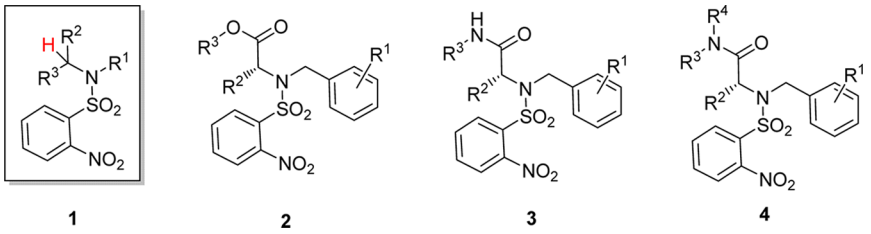


Figure 1. Structures of model compounds.

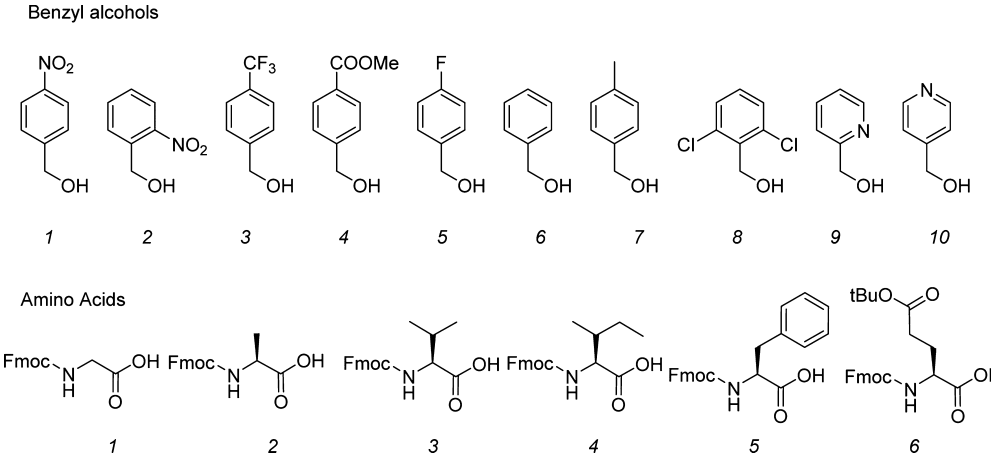


Figure 2. Structures and numbering of building blocks.

catalyzed ring expansion of 2*H*-indazole 1-oxides prepared from Gly provided access to quinazolines.[12] An analogous C-arylation was also reported using 4-Nos derivatives for the synthesis of C-α-aryl amino acids.[13,14]

Thus, far, we have studied the C-arylation of *N*-(2-arylethyl-2-oxo) and *N*-(2-methoxy-2-oxoethyl) derivatives prepared by the alkylation of polymer-supported 2-Nos sulfonamides with bromoketones and bromoacetates. Here, we expanded our work and addressed the general structural requirements for facilitating and directing the Nos amide-based intramolecular arylation. Different arylated products were obtained, depending on the substitution pattern, type of linker, acidity of the hydrogen on the benzyl methylene, and steric hindrance of the substituents.

RESULTS AND DISCUSSION

Design of Model Compounds. Figure 1 shows the generic structure of 2-nitrobenzenesulfonamides **1**, which are amenable to base-mediated intramolecular arylation. The key structural element is the acidic proton on the α-carbon. In our previous work, we studied the C-arylation (and subsequent nitrogenous heterocycle formation) of substrates **1** with R^2 = CH_2-CO-Ar or CH_2-COOMe and R^3 = H.[8−12] Our recent results indicated that *N*-benzyl derivatives **1** with R^2 = Ar and R^3 = H can also be arylated at the sp^3 carbon when strong electron-withdrawing groups are present on the aromatic ring (2- or 4-NO_2, 4-CF_3, 4-COOMe, or 2- or 4-pyridyl derivatives).[15]

Here, we focused on determining the structural and electronic features that direct arylation with the *N*-benzyl derivatives of amino acid esters **2**, amino acid secondary amides **3**, and amino acid tertiary amides **4**. *N*-Benzyl derivatives allowed the introduction of different R^1 aryl substituents; thus, electron-donating and electron-withdrawing substituents on the aromatic ring were fine-tuned to study the effects on the arylation reaction. We used 2-Nos sulfonamides rather than 4-Nos or other derivatives because we had previously observed that the C-arylated compounds could be converted to various nitrogenous heterocycles.[8−12]

The *N*-benzyl sulfonamides **2**−**4** contain two potential arylation sites; the arylation can occur on the benzyl sp^3 carbon or on the amino acid C^{α}. Tuning the combination of R^1 and R^2 substituents can redirect the arylation site and provide intermediates for the synthesis of diverse heterocycles.

Synthesis of Model Compounds. Amino acids were immobilized via ester (**5**), secondary amide (**6**), and tertiary amide (**7**) linkages. The esters **5** were synthesized on a 2-aminoethanol linker that allowed acid-mediated cleavage from

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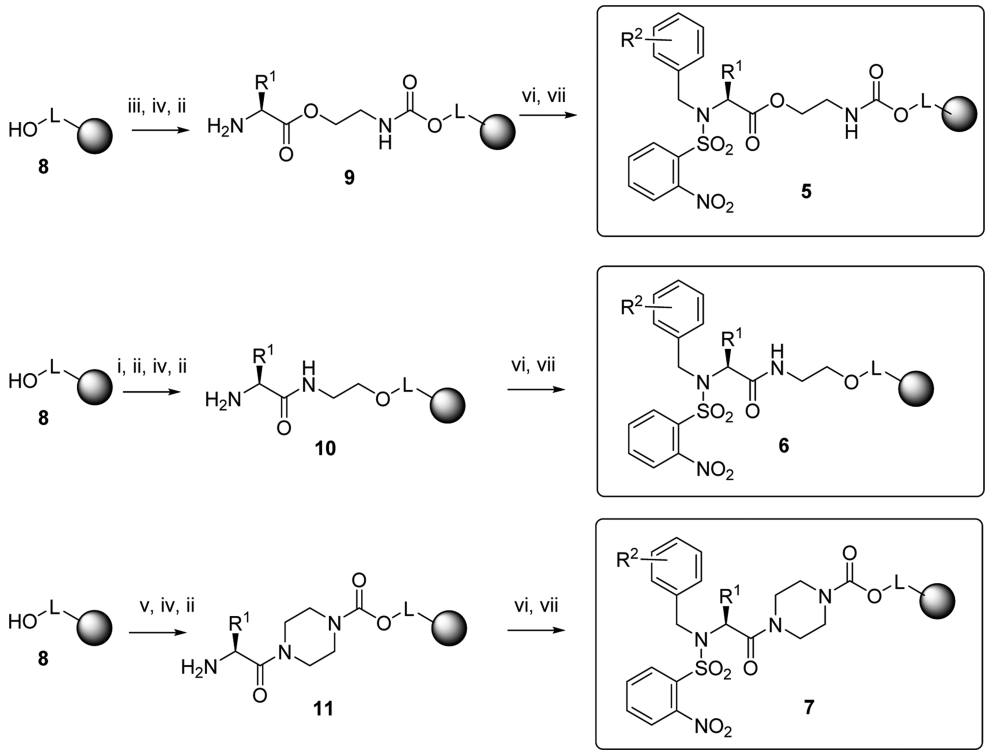
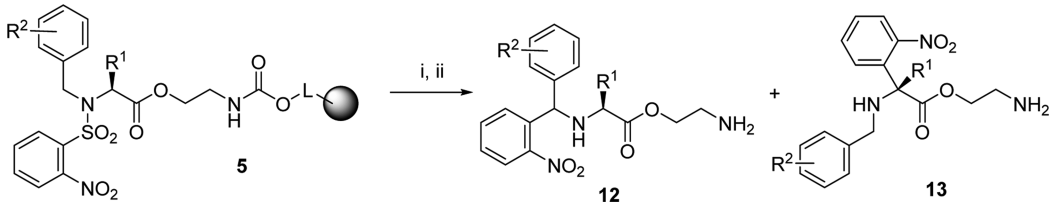
Scheme 2. Synthesis of Model Compounds[a]



[a]Reagents and conditions: (i) CCl_3CN, DBU, dichloromethane (DCM), 1 h, then Fmoc-ethanolamine, $BF_3{\cdot}Et_2O$, THF, 30 min; (ii) piperidine, DMF, 15 min; (iii) CDI, pyridine, DCM, 2 h, then ethanolamine, 16 h; (iv) Fmoc-amino acid, HOBt, DIC, DMAP (only for **9**), 1:1 DCM/DMF, 16 h; (v) CDI, pyridine, DCM, 2 h, then piperazine, 16 h; (vi) 2-Nos-Cl, 2,6-lutidine, DCM, 16 h; (vii) benzyl alcohols **1**−**7** or pyridylmethanols **8** and **9**, PPh_3, DIAD, THF, 2 h.

Scheme 3. C-Arylation of Ester Dual Substrates[a]



[a]Reagents and conditions: (i) DBU, DMF, rt, 16 h; (ii) 50% TFA in DCM, 1 h.

the Wang carbamate linker as well as nucleophilic cleavage (sodium hydroxide). Briefly, Wang resin[16] **8** was derivatized with 2-(Fmoc-amino)ethanol via an ether linkage through trichloroacetimidate activation,[17] and the Fmoc group was cleaved with piperidine. Wang resin was also functionalized with 2-aminoethanol (for resins **6**) and piperazine (for resins **7**) through carbamate formation[18] via 1,1′-carbonyldiimidazole (CDI) activation. The polymer-supported alcohol and two amines were acylated with Fmoc-amino acids using a standard *N*,*N*′-diisopropylcarbodiimide (DIC) and *N*-hydroxybenzotriazole (HOBt) method; for esterification, DMAP was added as a catalyst. After the Fmoc group had been removed, the resin-bound amines **9**−**11** were reacted with 2-Nos-Cl. Subsequent Fukuyama alkylation[3] under Mitsunobu conditions[19,20] with a range of benzyl alcohols (Figure 2) afforded the key model compounds, **5**−**7** (Scheme 2).

Ester-Based Dual Substrates. Ester-based model compounds **5** provide two positions for potential arylation, the benzylic sp^3 carbon, which yielded **12**, and the α-carbon of the amino acid, which yielded **13** (Scheme 3). First, we addressed the effect of the amino acid (R^1) on the intramolecular arylation of model compounds prepared with 2-nitrobenzyl alcohol. DBU exposure of all substrates **5** resulted in benzylic sp^3 carbon arylation with the exception of Ala derivative **5**{2,2} (Table 1). With Ala derivative **5**{2,2}, we obtained a mixture of α-carbon-arylated **13** and benzylic sp^3-arylated products **12**. The incorporation of more bulky side chains directed arylation to the benzylic sp^3 carbon, and benzhydrylamines **12** were the only arylation products isolated. All reactions were performed at room temperature (rt) and provided highly pure crude products (75%−94%). Benzhydrylamines **12** represent advanced intermediates for the synthesis of quinazolinones via indazole oxides,[12] and the partial transformation of Gly derivative **12**{1,2} to quinazolinones was observed. The conversion of other derivatives **12** to quinazolinones required elevated temperatures.

Because only derivative **5**{2,2} provided a mixture of arylated products, we used the Ala-derived model compound to evaluate

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Table 1. C-Arylation of Ester-Based Dual Substrates

resin	NH-CHR[1]-CO	R^2	**12**[a] (%)	**13**[a] (%)	yield[b] (%)
		Effect of the Amino Acid			
5{1,2}	Gly	2-NO_2	59[c]	<1	18
5{2,2}	Ala	2-NO_2	78	22	*d*
5{3,2}	Val	2-NO_2	96	<1	34
5{4,2}	Ile	2-NO_2	95	<1	51
5{5,2}	Phe	2-NO_2	92	<1	41
5{6,2}	Glu	2-NO_2	89	<1	38
		Effect of the Benzyl Alcohol			
5{2,2}	Ala	2-NO_2	78	22	*d*
5{2,3}	Ala	4-CF_3	<1	89	80
5{2,4}	Ala	4-COOMe	<1	87	76
5{2,5}	Ala	4-F	<1	91	62
5{2,6}	Ala	H	<1	94	86
5{2,8}	Ala	2,6-diCl	<1	84	70
5{2,9}	Ala	2-Py	<1	90	86
5{2,10}	Ala	4-Py	<1	89	65

[a]Analysis of crude products by liquid chromatography at 210−500 nm. [b]Isolated yield after high-performance liquid chromatography purification. [c]Partially cyclized (41%) to quinazoline **12Q**, in an isolated yield of 3.1 mg (7.5%) (cf. Experimental Section). [d]Compound **12**, yield 21%; compound **13**, yield 6.6%.

Table 2. C/N-Arylation of Amide-Based Dual Substrates

resin	NH-CHR[1]-CO	R^2	*T*	time	**14**[a] (%)	**15**[a] (%)	yield[b] (%)
		Effect of the Amino Acid					
6{1,1}	Gly	4-NO_2	rt	30 min	38	<1	39
6{1,3}	Gly	4-CF_3	rt	on	<1	29[c]	NI
6{2,2}	Ala	2-NO_2	rt	on	87	<1	18
6{3,2}	Val	2-NO_2	rt	on	67	<1	67
		Effect of the Benzyl Alcohol					
6{2,5}	Ala	4-F	rt[d]	on	<1	77	29
6{2,6}	Ala	H	rt[d]	on	<1	72	25
6{2,8}	Ala	2,6-diCl	rt	on	<1	88	36
6{2,9}	Ala	2-Py	rt	on	<1	55	17
6{3,6}	Val	H	80 °C	on	<1	50	54

[a]The purity of crude products was estimated from crude traces at 210−500 nm. [b]Isolated yield after high-performance liquid chromatography purification. [c]Arylation incomplete, contained 68% sulfonamide. [d]Analytical sample, preparation at 80 °C; NI, not isolated because of co-elution of sulfonamide **6** and N-aryl derivative **15**.

the effect of aromatic ring substituents. All model compounds prepared with different benzyl alcohols were arylated only at the amino acid carbon. At this stage, we did not address the optical integrity of compounds **12**; an analogous arylation was reported with 4-Nos derivatives and included an assessment of the stereoselectivity of the arylation.[13,14] Quaternary carbon derivatives **13** are particularly attractive as intermediates for the synthesis of 3-amino-2-oxindoles.[21]

Secondary Amide-Based Dual Substrates. In comparison to the previously discussed esters **5**, we observed remarkably different results for DBU-mediated arylation with the secondary amide-based substrates. No arylation of the amino acid α-carbon occurred with any model compound. Instead, we observed the formation of N-aryl derivatives (Scheme 4). The result of DBU exposure to polymer-supported sulfonamides **6** was dependent on the substituents on the benzyl ring, and we observed either C-arylation (**14**) or N-arylation (**15**) (Table 2). In the case of Ala-based derivatives, the presence of the strongly electron-withdrawing nitro group directed arylation to the benzylic sp^3 carbon. With weaker electron-withdrawing substituents, we observed only N-arylation and the formation of 2-nitroaniline derivatives **15**. The N-aryl derivatives **15** are practical resin-bound intermediates for the synthesis of quinoxalinones using a recently reported amide linker-based cyclative cleavage.[22]

In contrast, C-aryl derivatives **14** can be transformed to quinazolines at elevated temperatures, analogous to the previously reported synthesis of quinazolines.[12]

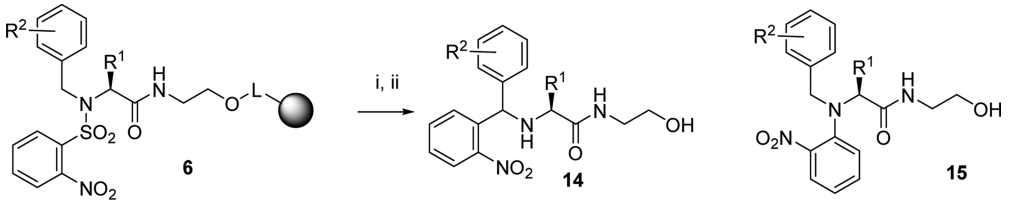
The mechanism of N-arylation can be explained by a Smiles-type rearrangement[23,24] (Scheme 5). The presence of the secondary amide is essential for this rearrangement. We did not observe N-arylation with the ester or tertiary amide model compounds.

Tertiary Amide-Based Dual Substrates. To verify that N-arylation involved the secondary amide, we prepared tertiary amide-containing compounds **7**. The absence of a proton at the amide nitrogen prevented Smiles-type rearrangement and subsequent formation of N-aryl derivatives. As expected, we observed arylation at the benzyl methylene carbon and the formation of compounds **16** prepared from 2-nitrobenzyl alcohol (Scheme 6). Unsubstituted or 4-methylbenzyl derivatives yielded α-carbon arylated compounds **17** (Table 3). Thus, the use of tertiary amide substrates **7** provided results analogous to those observed for ester-based model compounds **5**; however, higher temperatures were required for arylation to proceed.

CONCLUSION

Resin-bound 2-alkyl-2-{[*N*-(benzyl)-2-nitrophenyl]-sulfonamido}acetic acid esters and amides underwent base-mediated intramolecular arylation. Alteration of the substitution pattern and carboxy-terminal functionality directed the site of arylation to the benzylic sp^3 carbon, the α-carbon of the amino acid, or the sulfonamide nitrogen. Arylation of the benzylic sp^3 carbon by 2-Nos amides occurred only when electron-

Scheme 4. Two Sites of Arylation in Secondary Amide Dual Models[a]



[a]Reagents and conditions: (i) DBU, DMF (for temperatures and times, see Table 2); (ii) 50% TFA in DCM, 1 h.

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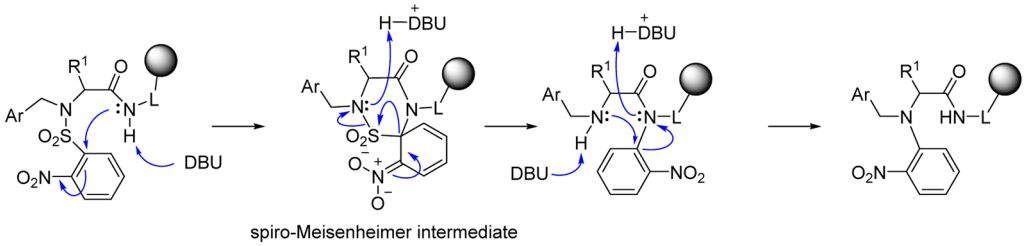
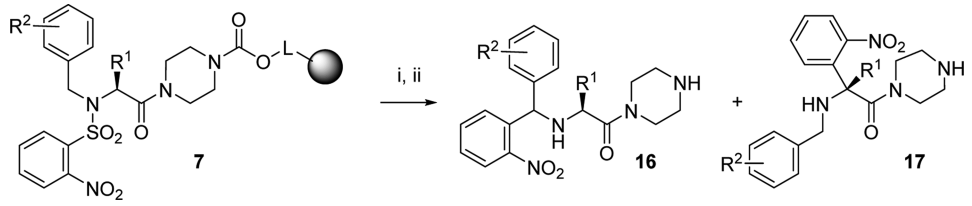
Scheme 5. Plausible Mechanism of N-Arylation



Scheme 6. C-Arylation of Tertiary Amide Dual Substrates[a]



[a]Reagents and conditions: (i) DBU, DMF (for temperatures and times, see Table 3), 16 h; (ii) 50% TFA in DCM, 1 h.

Table 3. C-Arylation of Tertiary Amide-Based Dual Substrates

resin	NH-CHR[1]-CO	R^2	T	time	**16**[a] (%)	**17**[a] (%)	yield[b] (%)
Effect of the Amino Acid							
7{1,1}	Gly	4-NO_2	rt	30 min	39	<1	58
7{2,2}	Ala	2-NO_2	rt	on	70	<1	35
7{3,2}	Val	2-NO_2	80 °C	on	36	<1	26
Effect of the Benzyl Alcohol							
7{2,3}	Ala	4-CF_3	80 °C	2 days	3	13	15
7{2,6}	Ala	H	80 °C	on	<1	58	76
7{2,7}	Ala	4-CH_3	80 °C	on	<1	74	63

[a]The purity of crude products was estimated from liquid chromatography traces at 210–500 nm. [b]Isolated yield after high-performance liquid chromatography purification.

withdrawing substituents were present on the aromatic ring. Model compounds containing two competitive arylation sites (α-carbon of an amino acid) underwent α-carbon arylation with esters and tertiary amides. N-Aryl derivatives were formed with secondary amides. Different routes of arylation provided advanced intermediates for the synthesis of diverse nitrogenous heterocycles, including indazoles, quinazolinones, quinoxalinones, and 3-amino-2-oxindoles. The synthesis of individual heterocycles will be reported in further communications.

EXPERIMENTAL SECTION

General. The solid-phase syntheses were performed in plastic reaction vessels (syringes equipped with one porous disk each) using a manually operated synthesizer.[25] The volume of the wash solvent was 10 mL per gram 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 with Nos-Cl. Resins **9**–**11** (1 g) were 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.

Reaction with Benzyl Alcohols (resins 5–7). Resins form the previous step (250 mg) were washed three times with anhydrous THF. A solution of benzyl alcohol (0.5 mmol) and triphenylphosphine (0.5 mmol, 131 mg) in 2 mL of anhydrous THF was added to the resin, which was subsequently left in a freezer for 30 min. A solution of DIAD (0.5 mmol, 96 μL) was then added, and the slurry was shaken at ambient temperature for 2 h. The resin was washed three times with THF and three times with DCM.

Reaction with DBU. Resins **5**–**7** (250 mg) were washed three times 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 or 80 °C (Tables 1–3). The resin was washed three times with DMF and three times with DCM.

Cleavage and Isolation (12–17). Resins from the previous step were treated with 50% TFA in DCM for 1 h. The TFA solution was collected; the resin was washed three times with 50% TFA in DCM, and the extracts were combined and evaporated by a stream of nitrogen. Oily products were dissolved in methanol (3 mL) and purified by semipreparative reverse-phase high-performance liquid chromatography.

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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REFERENCES

(1) Schreiber, S. L. Target-oriented and Diversity-oriented Organic Synthesis in Drug Discovery. *Science* **2000**, *287*, 1964−1969.
(2) Cankarova, N.; Krchnak, V. Solid-Phase Synthesis Enabling Chemical Diversity. In *Diversity-Oriented Synthesis: Basics and Applications in Organic Synthesis, Drug Discovery, and Chemical Biology*; Trabocchi, A., Ed.; Wiley: New York, 2013; pp 201−252.
(3) Fukuyama, T.; Jow, C. K.; Cheung, M. 2- and 4-Nitrobenzenesulfonamides: Exceptionally Versatile Means for Preparation of Secondary Amines and Protection of Amines. *Tetrahedron Lett.* **1995**, *36*, 6374−6377.
(4) Kan, T.; Fukuyama, T. Ns Strategies: A Highly Versatile Synthetic Method for Amines. *Chem. Commun.* **2004**, 353−359.
(5) Yang, L.; Chiu, K. Solid Phase Synthesis of Fmoc N-Methyl Amino Acids: Application of the Fukuyama Amine Synthesis. *Tetrahedron Lett.* **1997**, *38*, 7307−7310.
(6) Lin, X.; Dorr, H.; Nuss, J. M. Utilization of Fukuyama's Sulfonamide Protecting Group for the Synthesis of N-Substituted α-Amino Acids and Derivatives. *Tetrahedron Lett.* **2000**, *41*, 3309−3313.
(7) Rew, Y.; Goodman, M. Solid-phase Synthesis of Amine-bridged Cyclic Enkephalin Analogues via On-resin Cyclization Utilizing the Fukuyama-Mitsunobu Reaction. *J. Org. Chem.* **2002**, *67*, 8820−8826.
(8) Bouillon, I.; Zajicek, J.; Pudelova, N.; Krchnak, V. Remarkably Efficient Synthesis of 2*H*-Indazole 1-Oxides and 2-*H*-Indazoles via Tandem Carbon-Carbon Followed by Nitrogen-Nitrogen Bonds Formation. *J. Org. Chem.* **2008**, *73*, 9027−9032.
(9) Pudelova, N.; Krchnak, V. Efficient Traceless Solid-Phase Synthesis of 3,4-Dihydropyrazino[1,2-b]indazoles and its 6-Oxides. *J. Comb. Chem.* **2009**, *11*, 370−374.
(10) Koci, J.; Krchnak, V. Solid-Phase Synthesis and Chemical Properties of 2-(2-Amino/hydroxyethyl)-1-aryl-3,4-dihydropyrazino-[1,2-b]indazol-2-iums. *J. Comb. Chem.* **2010**, *12*, 168−175.
(11) Koci, J.; Oliver, A. G.; Krchnak, V. Unprecedented Rearrangement of 1,2,3,4-Tetrahydropyrazino[1,2-*b*]indazole Oxides to 2,3-Dihydro-1*H*-imidazo[1,2-*b*]indazoles. *J. Org. Chem.* **2010**, *75*, 502−505.
(12) Krupkova, S.; Slough, G. A.; Krchnak, V. Synthesis of Quinazolines from *N*-(2-nitrophenylsulfonyl)iminodiacetate and α-(2-Nitrophenylsulfonyl)amino Ketones via 2*H*-Indazole 1-Oxides. *J. Org. Chem.* **2010**, *75*, 4562−4566.
(13) Lupi, V.; Penso, M.; Foschi, F.; Gassa, F.; Mihali, V.; Tagliabue, A. Highly Stereoselective Intramolecular α-Arylation of Self-stabilized Non-racemic Enolates: Synthesis of α-Quaternary α-Amino Acid Derivatives. *Chem. Commun.* **2009**, 5012−5014.
(14) Wilson, M. W.; Ault-Justus, S. E.; Hodges, J. C.; Rubin, J. R. A Facile Rearrangement of N-Alkyl, N-(o- or p-Nitrophenylsulfonamide)-α-Amino Esters. *Tetrahedron* **1999**, *55*, 1647−1656.
(15) Kisseljova, K.; Smyslova, P.; Krchnak, V. Base-mediated Intramolecular sp^3 C-Arylation of N-Benzyl-2-nitrobenzenesulfonamides: Advanced Intermediates for Synthesis of Indazoles and Quinazolines. *ACS Comb. Sci.*, under review.
(16) Wang, S.-S. p-Alkoxybenzyl Alcohol Resin and p-Alkoxybenzyloxycarbonylhydrazide Resin for Solid phase Synthesis of Protected Peptide Fragments. *J. Am. Chem. Soc.* **1973**, *95*, 1328−1333.
(17) Yan, L. Z.; Mayer, J. P. Use of Trichloroacetimidate Linker in Solid-phase Peptide Synthesis. *J. Org. Chem.* **2003**, *68*, 1161−1162.
(18) Letsinger, R. L.; Kornet, M. J.; Mahadevan, V.; Jerina, D. M. Reactions on Polymer Supports. *J. Am. Chem. Soc.* **1964**, *86*, 5163−5165.
(19) Mitsunobu, O.; Yamada, M. Preparation of Esters of Phosphoric Acid by the Reaction of Trivalent Phosphorus Compound with Diethyl Azodicarboxylate in the Presence of Alcohols. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 935−939.
(20) Mitsunobu, O. The Use of Diethyl Azodicarboxylate and Triphenylphosphine in Synthesis and Transformation of Natural Products. *Synthesis* **1981**, 1−28.
(21) O'Connor, S. J.; Liu, Z. A Concise Synthesis of Sterically Hindered 3-Amino-2-oxindoles. *Synlett* **2003**, 2135−2138.
(22) Neagoie, C.; Krchnak, V. Piperazine Amide Linker for Cyclative Cleavage from Solid Support: Traceless Synthesis of Dihydroquinoxalin-2-ones. *ACS Comb. Sci.* **2012**, *14*, 399−402.
(23) Levy, A. A.; Rains, H. C.; Smiles, S. The Rearrangement of Hydroxy-sulphones. Part I. *J. Chem. Soc.* **1931**, 3264−3269.
(24) Kleb, K. G. New Rearrangement of Smiles Reaction Type. *Angew. Chem., Int. Ed.* **1968**, *7*, 291.
(25) Krchnak, V.; Padera, V. The Domino Blocks: A Simple Solution for Parallel Solid Phase Organic Synthesis. *Bioorg. Med. Chem. Lett.* **1998**, *22*, 3261−3264.