ACS Combinatorial Science

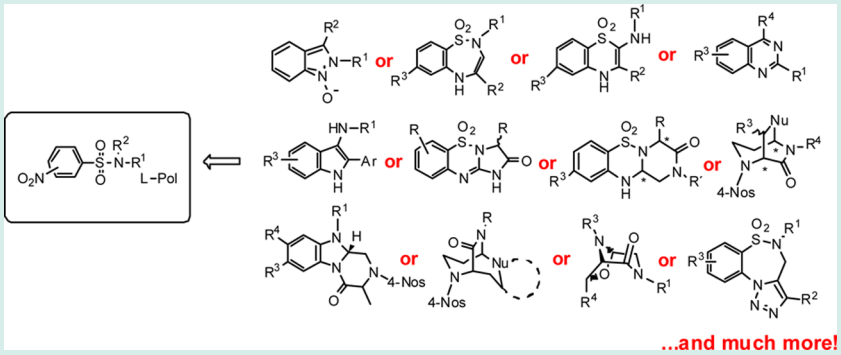
Review

pubs.acs.org/acscombsci

Mining the Chemical Space: Application of 2/4-Nitrobenzenesulfonamides in Solid-Phase Synthesis

Veronika Fülöpová and Miroslav Soural*

Department of Organic Chemistry, Institute of Molecular and Translational Medicine, Faculty of Science, Palacky University, 17 listopadu 12, 771 46 Olomouc, Czech Republic



ABSTRACT: Polymer-supported benzenesulfonamides prepared from various immobilized primary amines and 2/4-nitrobenzenesulfonyl chloride have been used as key intermediates in different chemical transformations, including unusual rearrangements to yield a number of diverse privileged scaffolds. This review summarizes individual strategies in their application to date.

KEYWORDS: *Fukuyama alkylation, Fukuyama–Mitsunobu alkylation, 2-nitrobenzenesulfonyl chloride, 4-nitrobenzenesulfonyl chloride, protective group, rearrangement, C-arylation, N-arylation, solid-phase synthesis*

INTRODUCTION

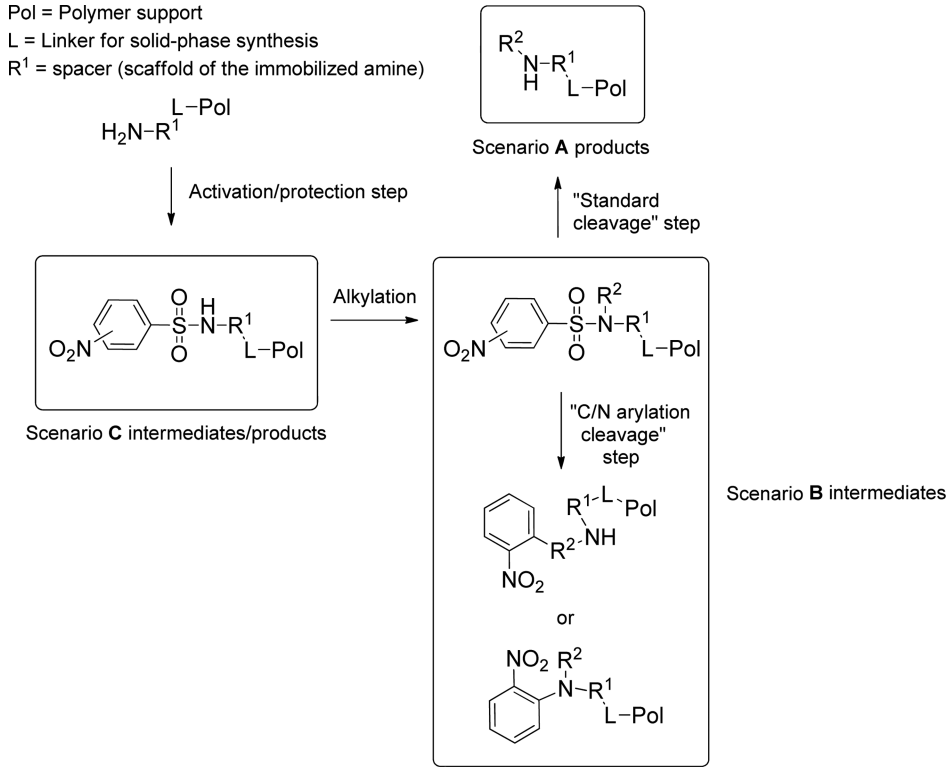
Compounds containing a benzenesulfonamide scaffold belong to the most intensively studied sulfurous organic derivatives. Their utility originated in the field of medicinal chemistry, which introduced benzenesulfonamides as pharmacologically important compounds.[1−4] A number of these molecules have applications in human medicine, particularly as potent antidepressant,[5] antitumor,[6−8] antiviral,[9] and antimicrobial[10,11] agents. In the field of synthetic organic chemistry, a special group of derivatives is represented by 2- and 4-nitrobenzenesulfonamides derived from primary amines. Such compounds are easily accessible from 2-nitrobenzenesulfonyl chloride (2-Nos-Cl) and 4-nitrobenzenesulfonyl chloride (4-Nos-Cl), respectively. In 1995, a milestone in nitrobenzenesulfonamide application in preparative synthesis was achieved by Fukuyama, who reported their use for the selective monoalkylation of primary amines.[12,13] Although alternative methods had been developed earlier (e.g., reductive alkylation or acylation followed by amide reduction),[14−16] the Fukuyama procedure quickly became the method of choice. Even strategies based on a similar approach using tosylamides and trifluoroacetamides could not compete with Fukuyama method because of the relatively harsh conditions needed to cleave the activating/protecting tosyl and trifluoroacetyl groups.[12] Alkylation of nitrobenzenesulfonamides with either alkyl halides, alcohols,[17,18] or α,β-unsaturated ketones (Michael addition)[19] is followed by cleavage of a Nos group under mild reaction conditions, typically using various thiols. Because of its simplicity and only few limitations,[20,21] the Fukuyama strategy has subsequently been employed by many chemists for the regioselective monoalkylation of diverse intermediates. In addition to traditional solution-phase synthesis, Fukuyama protection/activation is also efficient in solid-phase synthesis (SPS) using an excess of alkylating species. Miller initially used this technique in 1997[22] to selectively N-methylate peptides. The mild cleavage conditions compared with alternative acid/base methods (such as Benoiton, Freidinger, or Grieco)[23] are preferred in SPS because they are compatible with a number of acid/base-labile linkers. For this reason, the Fukuyama alkylation method significantly impacted solid-phase synthesis in the following decade.

In 2008, solid-phase Fukuyama alkylation with haloketones unexpectedly provided novel indazole-*N*-oxide derivatives.[24] Rearrangement was based on C-arylation followed by cleavage of the sulfur dioxide moiety. This discovery ushered in a new era of Nos-Cls in organic synthesis. Instead of the standard Fukuyama alkylation, nitrobenzenesulfonamides have been advanced intermediates in diversity-oriented synthesis (DOS) of various heterocyclic scaffolds.[25] Later research showed that intramolecular

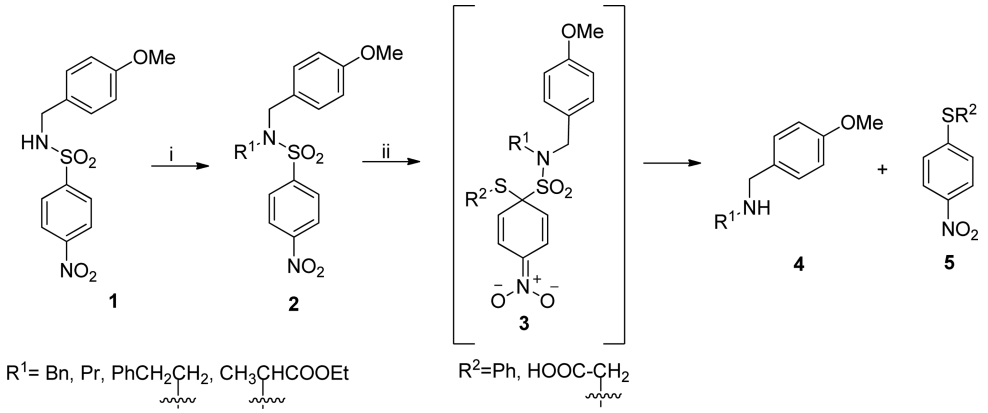
Received: June 5, 2015
Revised: July 30, 2015
Published: September 1, 2015

DOI: 10.1021/acscombsci.5b00089
ACS Comb. Sci. 2015, 17, 570−591

Scheme 1. Three Different Scenarios for Application of Nos-Cls in Solid-Phase Synthesis



Scheme 2. Mechanism of Nos Deprotection According to Fukuyama[12] (Demonstrated for 4-Nos)[a]



[a]Reagents: (i) R^1OH, diethyl azodicarboxylate (DEAD), triphenylphosphine (PPh_3), DCM or R^1X, K_2CO_3, DMF; (ii) R^2SH, K_2CO_3, DMF.

N-arylations can also occur, depending on the type of substrate and the reaction conditions.[26] Apart from planar heterocyclic scaffolds, compounds with three-dimensional (3D) architecture (the presence of sp^3 carbons) and derivatives with stereoselective formation of stereogenic centers were also accessible to cover a larger part of the chemical space.

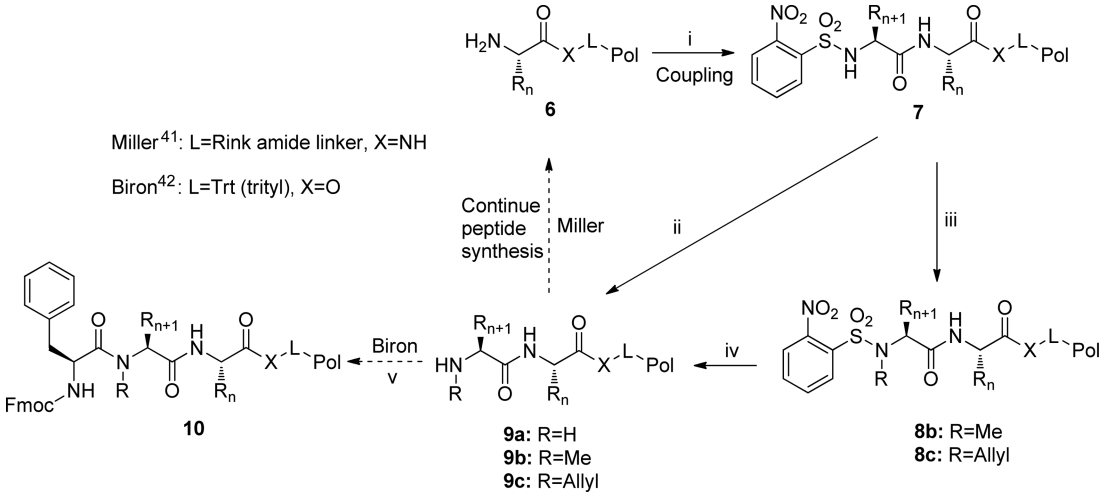
This review summarizes the entire history of polymer-supported 2- and 4-nitrobenzensulfonamides. Three general different approaches are distinguished (Scheme 1): (i) Nos as a standard protecting group for monoalkylation followed by cleavage of the Nos group (scenario A), (ii) Nos as an activation species for Fukuyama or Fukuyama−Mitsunobu alkylation while preserving the Nos scaffold (or just the aromatic portion) in the final structure (scenario **B**), and (iii) Nos-Cls as common building blocks without application of Fukuyama alkylation (scenario **C**).

1. SCENARIO A: PROTECTING/ACTIVATING FUNCTION FOR THE REGIOSELECTIVE ALKYLATION

Incorporation of the Nos group to obtain the corresponding nitrobenzenesulfonamide is typically carried out with Nos-Cl in the presence of base (e.g., collidine, *N*,*N*-diisopropylethylamine (DIEA), triethylamine (TEA), or 2,6-lutidine)[27−30] in different solvents such as *N*,*N*-dimethylformamide (DMF), tetrahydrofuran (THF), or dichloromethane (DCM). The resulting nitrobenzenesulfonamide intermediate is subjected to alkylation with different species followed by deprotection of the Nos moiety. In addition to its protecting/activating function, the most important feature of the Nos group is its mild cleavage conditions. In accordance with the original Fukuyama procedure (Scheme 2),[12] deprotection of intermediate **2** is mediated by diverse thiols (e.g., thiophenol, mercaptoethanol, mercaptoacetic acid, 1*H*,1*H*,2*H*,2*H*-perfluorodecane-1-thiol, or

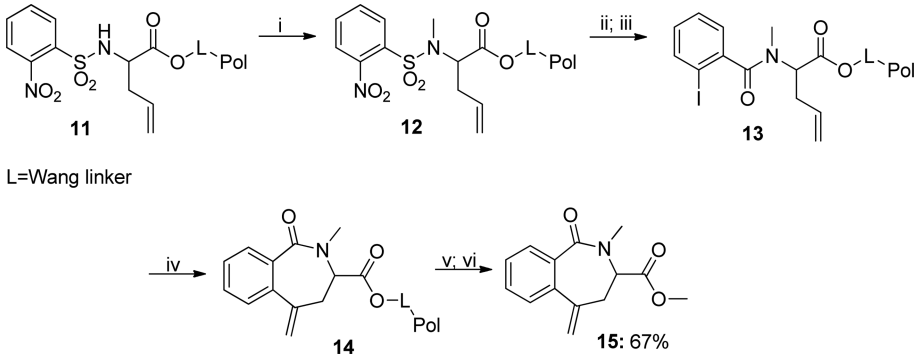
DOI: 10.1021/acscombsci.5b00089
ACS Comb. Sci. 2015, 17, 570−591

Scheme 3. Use of *N*-2-Nos-Protected Amino Acids in Peptide Synthesis[a]



[a]Reagents: (i) 2-Nos-AA-OH or 2-Nos-Phe-Cl, *N*,*N*,*N*′,*N*′-tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uranium hexafluorophosphate (HBTU), *N*-methylmorpholine (NMM), DMF; (ii) PhSH, K_2CO_3, DMF; (iii) (a) methyl 4-nitrobenzenesulfonate, 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD), dimethylacetamide (DMA) or (b) allyl methyl carbonate, $Pd_2(dba)_3$, $CHCl_3$, PPh_3, THF; (iv) 2-mercaptoethanol, DBU, DMF; (v) Fmoc-Phe-OH, 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxide hexafluorophosphate (HATU), 1-hydroxy-7-azabenzotriazole (HOAt), DIEA, NMP.

Scheme 4. Fukuyama Methylation of the Unnatural Amino Acid Sulfonamide for the Heck Reaction[a]



[a]Reagents: (i) MTBD, MeI, DMF; (ii) PhSH, K_2CO_3, DMF; (iii) 2-iodobenzoyl chloride, TEA, DCM; (iv) $Pd(OAc)_2$, PPh_3, Bu_4NCl, potassium acetate, DMF, 70 °C; (v) 50% trifluoroacetic acid (TFA) in DCM; (vi) CH_2N_2.

2,2′-(ethylenedioxy)diethanethiol)[31−36] in the presence of a suitable base, such as potassium carbonate, collidine, propylamine, or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), via Meisenheimer complex **3**. A specific area is represented by the application of polymer-supported thio derivatives.[37−39] The typical solvent for the deprotection step is DMF or *N*-methylpyrrolidone (NMP). Ionic liquids[40] have also been used in solution-phase chemistry. However, the most frequently applied procedure in SPS consists of the combination of mercaptoethanol, DBU, and DMF.

In the context of scenario A, the following subchapters summarize the individual approaches sorted according to the type of alkylating agent.

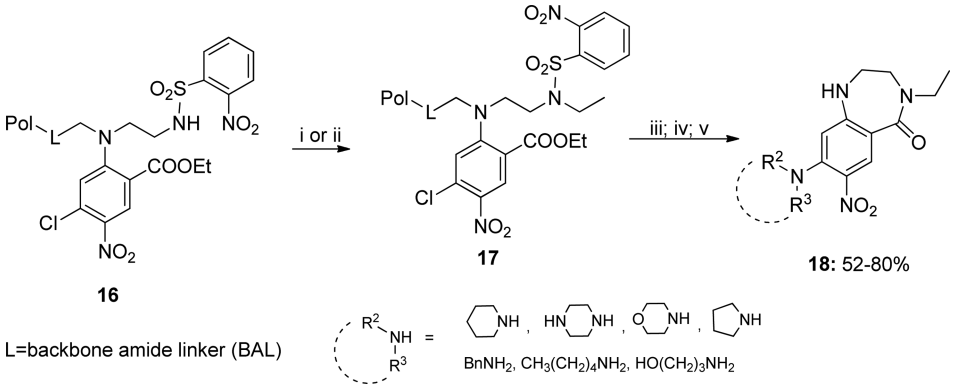
1.1. Alkylation with Alkyl Halides or (Pseudo)halides. The historical solid-phase Fukuyama alkylation belongs in this category.[22] Miller and Scalan automated the SPS of a thrombin receptor agonist peptide amide (SFLLRN) with the cheaper *N*-2-Nos-protected N-unalkylated amino acid in place of the commonly applied *N*-(9-fluorenylmethoxycarbonyl)amino acid (Fmoc-AA-OH).[41] In contrast to Fmoc deprotection, cleavage of the 2-Nos group of peptide **7** by thiophenol produced compound **9a** and a yellow chromophore, which allowed the process to be inspected visually (Scheme 3). To expand the developed method, the starting *N*-2-Nos peptide **7** underwent selective N-alkylation (**8b**) or N-allylation (**8c**) prior to deprotection. After selective removal of the Nos group from compound **8b**, the subsequent coupling of immobilized N-alkylated peptide **9b** with 2-Nos-AA-OH was effortless. On the other hand, coupling of N-allylated peptide **9c** with 2-nosyl amino acid (2-Nos-AA-OH) was more complicated because of the formation of side products. To increase the coupling yield, peptide **9c** was coupled with 2-Nos-AA-Cls. The developed strategy is compatible with the Fmoc protecting group and can therefore also be combined with Fmoc-AA-OH.[42]

The methylation of non-natural α-amino acids was described by Bolton and Hodges,[43] who developed a procedure for the intramolecular Heck cyclization of solid-supported allyl intermediates **13**. *N*-Methylsulfonamide **12** was deprotected by thiolate and then acylated with 2-iodobenzoyl chloride (Scheme 4). The final Heck cyclization of **13** was accomplished under Pd(II) catalysis.

In addition to solid-supported α-amino acids, alkylation of other immobilized amines has also been described.[44] The following example shows the alkylation of 1,2-diaminoethane

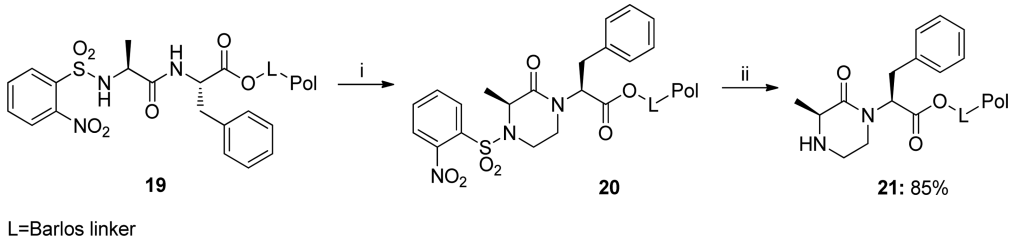
DOI: 10.1021/acscombsci.5b00089
ACS Comb. Sci. 2015, 17, 570−591

Scheme 5. Use of the Nos Protecting Group for the Alkylation of Immobilized Diamines[a]



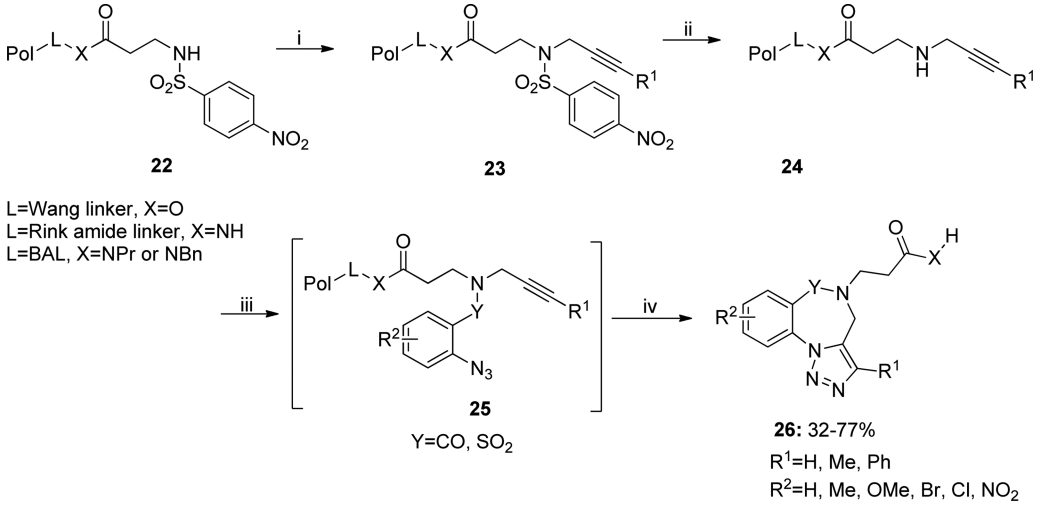
[a]Reagents: (i) ethyl iodide, DBU, DMF; (ii) EtOH, diisopropyl azodicarboxylate (DIAD), PPh_3, anhydrous THF; (iii) amine, dimethyl sulfoxide (DMSO), microwave (200 W, 150 °C); (iv) 2-mercaptoethanol, DBU, DMF; (v) 50% TFA in DCM.

Scheme 6. Intramolecular Alkylation of a Nos-Protected Dipeptide with 1,2-Dibromoethane[a]



[a]Reagents: (i) 1,2-dibromoethane, K_2CO_3, DMF, 60 °C; (ii) DBU, 2-mercaptoethanol, DMF.

Scheme 7. Intramolecular Cyclization via 1,3-Dipolar Cycloaddition[a]



[a]Reagents: (i) propargyl bromide, DBU, DMSO; (ii) 2-mercaptoethanol, DBU, DMF; (iii) 2-azidobenzoic acid (Y = CO), 1-hydroxybenzotriazole hydrate (HOBt), *N,N'*-diisopropylcarbodiimide (DIC) or 2-azidobenzenesulfonyl chloride (Y = SO_2), 2,6-lutidine, DCM; (iv) 50% TFA in DCM.

intermediate **16**, which spontaneously afforded solid-supported benzodiazepinone derivatives **18** after cleavage of the Nos group (Scheme 5).

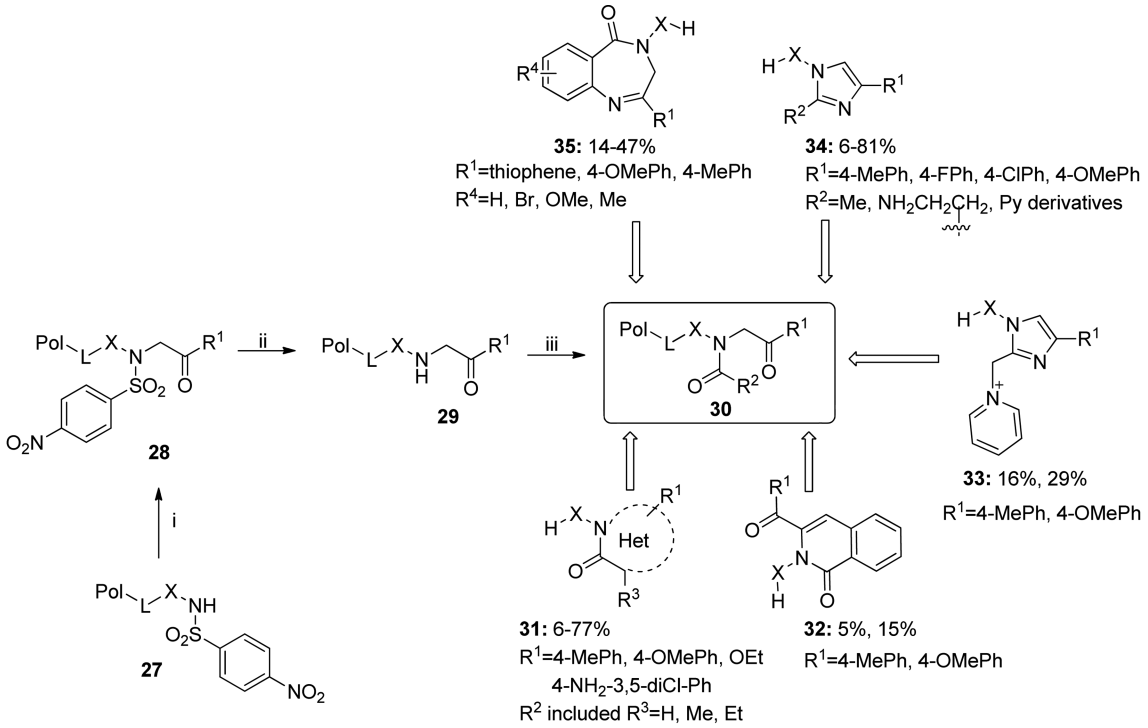
Functionalized alkyl halides have been used to construct additional heterocyclic scaffolds. For example, N-alkylation of immobilized Nos-dipeptide **19** with 1,2-dibromoethane was followed by spontaneous intramolecular cyclization to yield *N*-2-Nos-oxopiperazines **20** (Scheme 6).[45] Cleavage of the 2-Nos group provided the target compounds **21**, which can be further derivatized with another amino acid.

Similarly, propargyl bromides were used to construct the 1,2,3-triazole scaffold. Intermediate **22** was alkylated with different substituted propargyl bromides, followed by deprotection of the 4-Nos group (Scheme 7).[46] Subsequent acylation of intermediate **24** with 2-azidobenzoic acids or 2-azidobenzenesulfonyl chloride spontaneously afforded benzotriazolodiazepinones and their sulfonyl analogues **26**.

In 2009, Pudelová and Krchňák[47] developed a DOS[48] of various heterocycles through α-acylamino ketone/ester intermediates **30** (Scheme 8). The starting 4-nitrobenzenesulfonamides **27** were

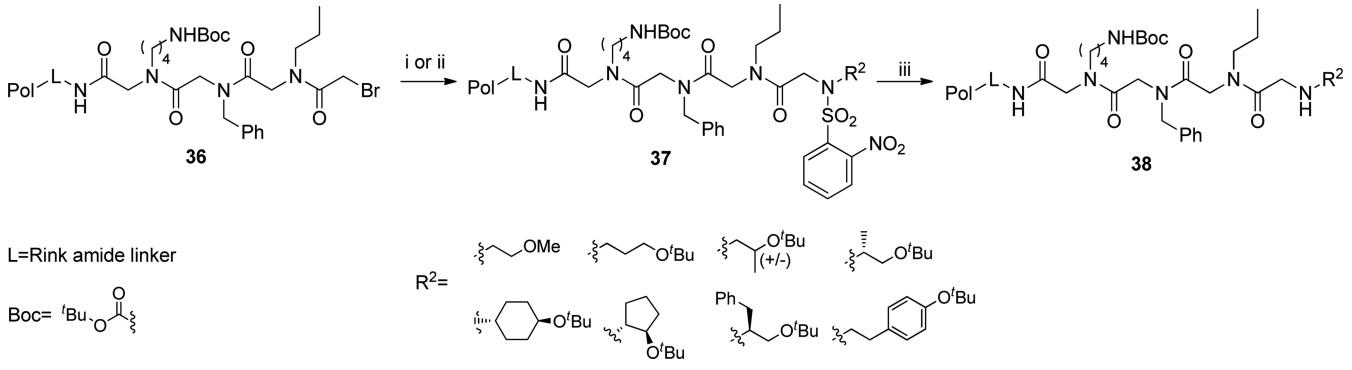
DOI: 10.1021/acscombsci.5b00089
ACS Comb. Sci. 2015, 17, 570−591

Scheme 8. Use of Nitrobenzenesulfonamides and Haloketones in the Synthesis of Different Nitrogenous Heterocycles[a]



[a]Reagents: (i) haloketone, DIEA, DMF; (ii) 2-mercaptoethanol, DBU, DMF; (iii) α-bromocarboxylic acid, DIC, DCM, DIEA or Fmoc-α-AA-OH, DIC, DCM/DMF or 2-nitrobenzoic acid, DIC, DMF.

Scheme 9. Reverse Alkylation of Nitrobenzenesulfonylamides with Polymer-Supported Halogenated Derivatives[a]



[a]Reagents: (i) 2-Nos-NHR^2, Cs_2CO_3, DMF (repeated once); (ii) 2-Nos-NHR^2, Cs_2CO_3, DMF, microwave (70 °C); (iii) *p*-OMePhSH, Cs_2CO_3 or DBU, DMF.

alkylated with different substituted α-haloketones. Deprotection of the Nos group and subsequent acylation of **29** with acids or their halogen derivatives provided the key intermediates **30**, which were subjected to different cyclization reactions leading to heterocycles **31**, **32**, and **33**. α-Acylamino ketones were also used to prepare trisubstituted 1*H*-imidazoles **34**.[49]

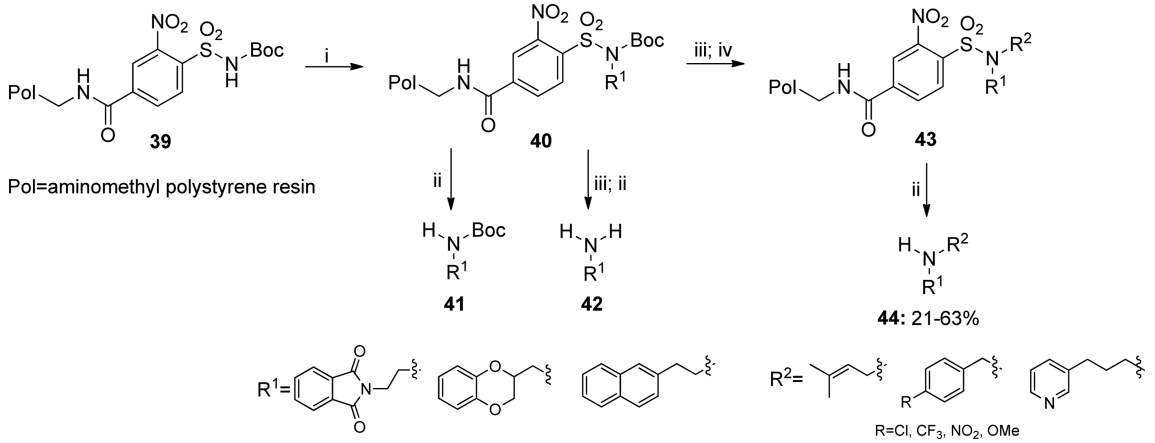
Recently, trisubstituted benzo[1,4]diazepin-5-one derivatives **35** were synthesized by a similar approach (Scheme 8).[50] Unlike the previous case, the deprotected precursor **29** was first acylated with 2-nitrobenzoic acid, and further reduction of the nitro group was followed by spontaneous intramolecular on-resin cyclization.

The analogous but reversed strategy was described by Biron and co-workers[51] for the synthesis of peptoids by an alternative path in the submonomer approach. This procedure utilized the alkylation of 2-nitrobenzenesulfonamide, prepared from 2-Nos-Cl, with immobilized bromoamide **36** (Scheme 9). Surprisingly, the common protocol for removing 2-Nos was not successful in this case. To avoid incomplete deprotection of intermediate **37**, Biron's group developed suitable conditions to use *p*-methoxybenzenethiol with Cs_2CO_3 or DBU.

1.2. Alkylation with Alcohols. The efficacy of Nos activation was significantly enhanced through use of the

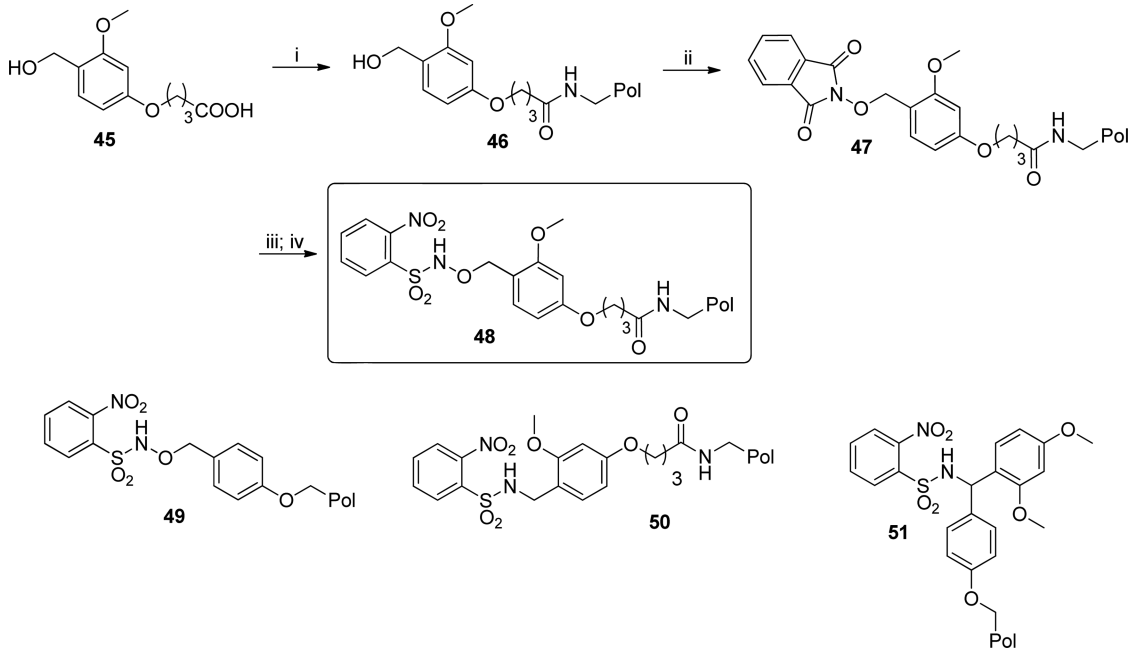
DOI: 10.1021/acscombsci.5b00089
ACS Comb. Sci. 2015, 17, 570−591

Scheme 10. *N*-Boc-2-nitrobenzenesulfonamide Linkers for the Preparation of Primary/Secondary Amines[a]



[a]Reagents: (i) R^1OH, PPh_3, DEAD, anhydrous THF; (ii) 2-mercaptoethanol, DBU, acetonitrile (MeCN); (iii) TFA, DCM; (iv) R^2OH, PPh_3, DEAD, anhydrous THF.

Scheme 11. Synthesis of the *N*-Benzyloxy-2-nitrobenzenesulfonamide Linker and Examples of Similar Individual Linkers[a]



[a]Reagents: (i) Aminomethylene PS/DVB resin, DIC, HOBt, DMF; (ii) *N*-hydroxyphthalimide, PPh_3, DIAD, anhydrous THF; (iii) 5% hydrazine hydrate, 50% THF in methanol (MeOH); (iv) Nos-Cl, 2,6-lutidine, DCM.

Mitsunobu reaction with alcohols as an alternative procedure to Fukuyama alkylation with alkyl halides. One of the first applications of the solid-phase Fukuyama–Mitsunobu procedure was described in 1997 by Murray and co-workers,[52] who later also developed *N*-Boc-2-nitrobenzenesulfonamide linkers **39** for the preparation of primary (**42**) and secondary (**44**) amines (Scheme 10).[53]

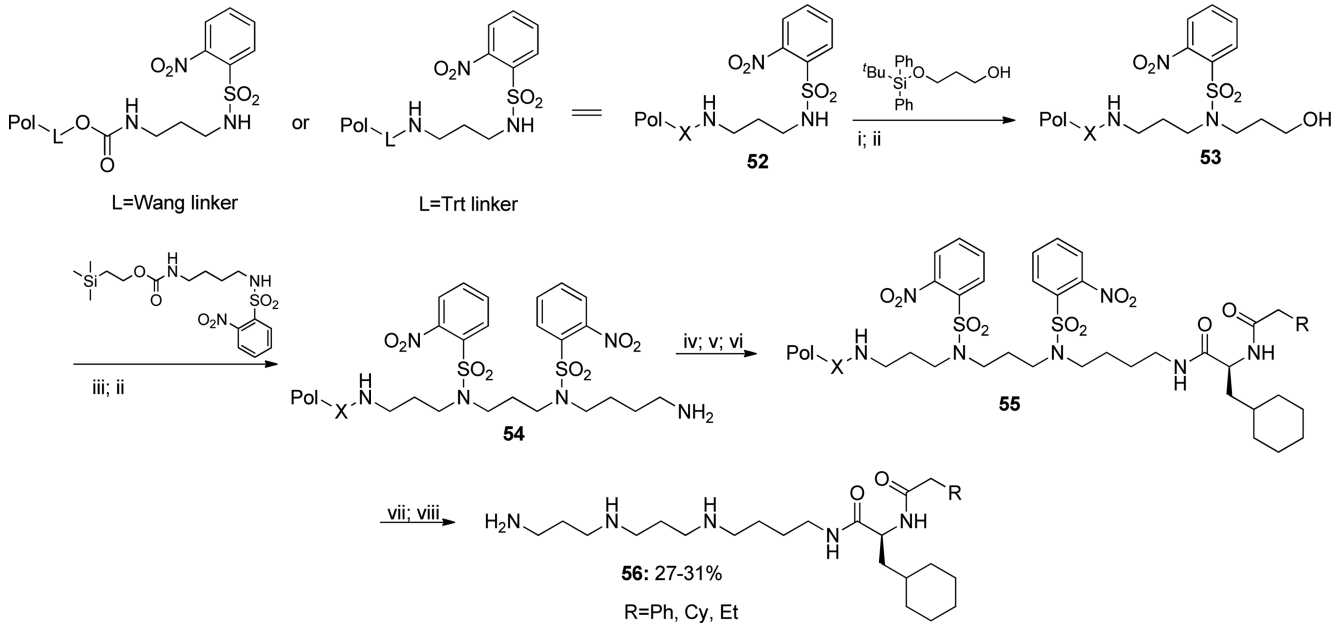
A similar approach developed a set of novel benzyloxy, benzylamine, and benzhydrylamine linkers.[19,54,55] Whereas linkers **48** and **49** have been designed for synthesis of *N*-alkyl and *N*-aryl hydroxamates (as discussed in subchapter 2.1, Scheme 24),[30] linkers **50** and **51** have been developed as an alternative to backbone amide linkers (BALs).[56] Scheme 11 depicts the individual types of linkers along with a representative example of the synthetic procedure. It is based on acylation of the aminomethylene polystyrene/divinylbenzene (PS/DVB) resin with 4-(4-hydroxymethyl-3-methoxyphenoxy)butyric acid (HMPB) linker **45** via HOBt activation. The subsequent Mitsunobu reaction of resin **46** with *N*-hydroxyphthalimide afforded intermediate **47**, which was cleaved with hydrazine and treated with 2-Nos-Cl to yield the resin-bound linker **48**.

Aside from monohydroxy derivatives, alkylation with diols has also been described. An example is given in Scheme 12, which shows the solid-phase synthesis of philanthotoxin-related compounds **56**.[57] Two alternative approaches were combined in the reaction sequence, Fukuyama–Mitsunobu alkylation with either solid-supported (step (i)) or solution-phase (step (iii)) nosylamides. To avoid potential cross-linking, the propylene glycol moiety was monoprotected by silylation.

As in the Fukuyama procedure with functionalized halides, diverse functionalized hydroxy derivatives have frequently been used to synthesize various heterocycles by

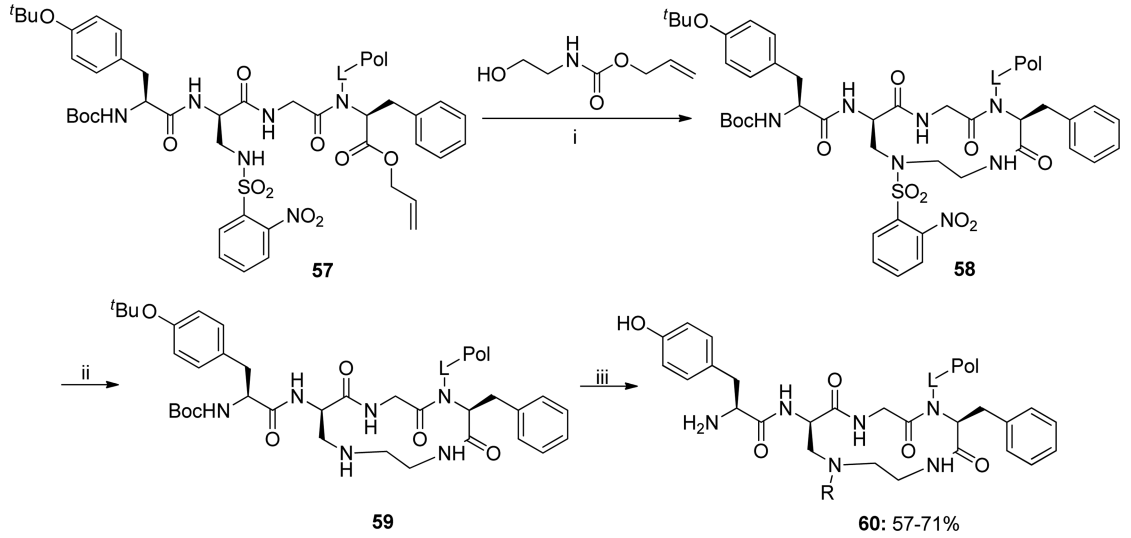
DOI: 10.1021/acscombsci.5b00089
ACS Comb. Sci. 2015, 17, 570–591

Scheme 12. Synthesis of Philanthotoxin-433 Analogues[a]



[a]Reagents: (i) PMe_3, 1,1′-(azodicarbonyl)dipiperidine (ADDP), THF, DCM, N_2; (ii) tetrabutylammonium fluoride (TBAF), THF, 50 °C; (iii) PBu_3, ADDP, THF, DCM, N_2; (iv) (*S*)-*N*-Fmoc-Cha-OPfp (Cha = cyclohexylalanine, Pfp = pentafluorophenyl), DIEA, 3,4-dihydro-5-hydroxy-4-oxo-1,2,3-benzotriazine (HODhbt), DMF, N_2; (v) 20% piperidine in DMF; (vi) $PhCH_2COOPfp$ or $CyCH_2COOPfp$ (Cy = cyclohexyl) or $C_3H_7COOPfp$, DIEA, HODhbt, N_2; (vii) 2-mercaptoethanol, DBU, DMF; (viii) TFA/DCM/triisopropylsilane/H_2O (47.5:47.5:2.5:2.5).

Scheme 13. Synthesis of Enkephalin Analogues[a]



[a]Reagents: (i) (a) DIAD, PPh_3, THF, (b) $PhSiH_3$, $Pd(PPh_3)_4$, DCM, (c) HBTU, HOBt, 2,6-lutidine, DCM/DMF (1:1); (ii) DBU, 2-mercaptoethanol, DMF; (iii) reductive amination, alkylation, or acylation to introduce the substituent R.

means of Fukuyama−Mitsunobu alkylation. For example, *N*-(allyloxycarbonyl)ethanolamine (*N*-Alloc-ethanolamine) was used in the SPS synthesis of enkephalin analogues (Scheme 13).[58] After alkylation of intermediate **57** with *N*-Alloc-ethanolamine and cleavage of the Alloc group, intermolecular cyclization promoted by HBTU/HOBt yielded the 13-membered cycle **58**. Deprotection of the 2-Nos group and introduction of the R substituent afforded the final compound **60**.

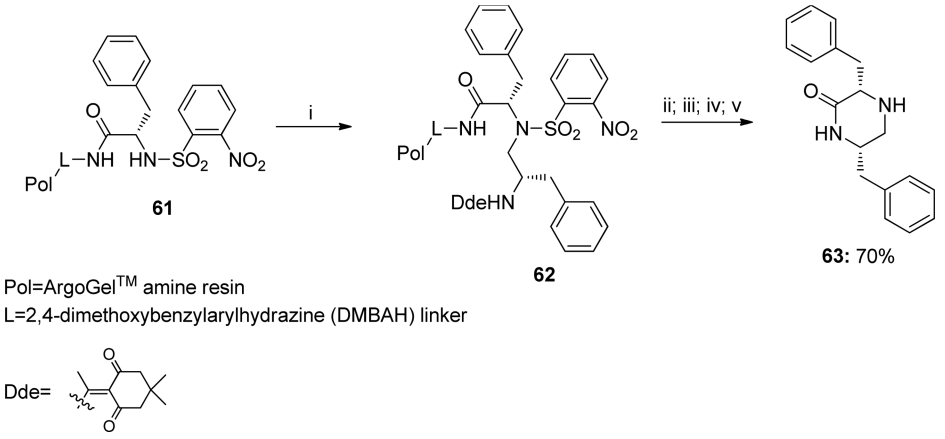
Ladlow showed that intramolecular cyclization can release the product from the resin (i.e., cyclative cleavage) when amino alcohols are involved.[59] Intermediate **61** was alkylated with *N*-Dde-phenylalaninol, and after cleavage of both protecting groups, the target monoketopiperazinone **63** was obtained (Scheme 14).

Alkylation with unsaturated alcohols yielded oxazepane derivatives **66** through C−C coupling.[60] The *N*-2-Nos-protected hydroxylamine intermediate **64** was reacted with but-3-en-1-ol derivatives, and subsequent intramolecular metathesis of compounds **65** under Ru(II) catalysis gave **66** (Scheme 15).

Recently, intermediates **67** with the aldehyde group protected as the acetal have been extensively employed in the alkylation of polymer-supported nitrobenzenesulfonamides. After cleavage from the polymer support with TFA, the unmasked aldehyde provides many different heterocyclic scaffolds via formation of

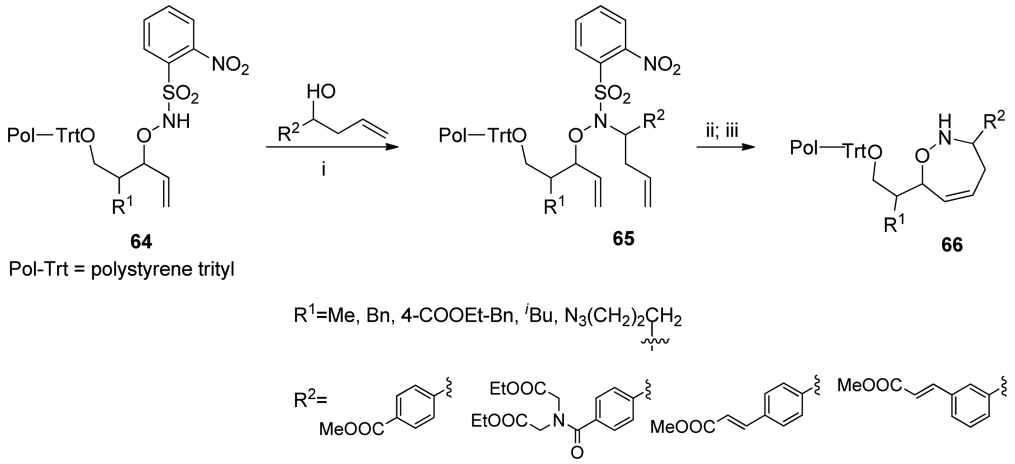
DOI: 10.1021/acscombsci.5b00089
ACS Comb. Sci. 2015, 17, 570−591

Scheme 14. Cyclative Cleavage after Fukuyama–Mitsunobu Alkylation[a]



[a]Reagents: (i) Ph_3P, tetrabutylammonium dodecanoate (TBAD), *N*-Dde-phenylalaninol, DCM; (ii) PhSNa, DMF; (iii) $N_2H_4{\cdot}H_2O$/DMF (1:5); (iv) 5% TFA in DCM; (v) $Cu(OAc)_2$, pyridine (Py), MeCN.

Scheme 15. Intramolecular Metathesis Leading to 1,2-Oxazepanes[a]



[a]Reagents: (i) PPh_3, $^iPrO_2C{-}N{=}N{-}CO_2{}^iPr$ or $^tBuO_2C{-}N{=}N{-}CO_2{}^tBu$, THF; (ii) $Cl_2Ru(PCy_3)_2{=}CHPh$, DCM; (iii) RSH, DBU, DCM, or NMP.

the corresponding iminium salts. This research has been primarily targeted at the incorporation of various heterocyclic scaffolds in a peptide backbone.[61−64] Representative examples are depicted in Scheme 16. In many cases, the Nos building block remains in the final structure, and these results are therefore also mentioned in the next chapter.

To access a new heterocyclic moiety through Nos activation, the functional group does not necessarily need to be introduced through external alkylation of a sulfonamide as in all of the previous cases. The following example demonstrates the activation of the amino group of intermediate **74** followed by attack of the neighboring alcohol, leading to the target tricyclic scaffold **76** (Scheme 17).[65]

Polymer-supported alcohols can be used similarly to immobilize alkyl halides (see Scheme 9) as the alkylation species. An example of this strategy has been already given in Scheme 12. Alternatively, Raveglia and co-workers[66] used reversed Mitsunobu alkylation (Scheme 18) to prepare amino intermediates **80**, which were later applied in the split-mix synthesis of a complex library with considerable diversity.

1.3. Alkylation with Unsaturated Ketones and Diazomethane. Apart from nucleophilic substitution with alcohols or alkyl halides, Michael addition of activated olefins can also incorporate N-substituents into nitrobenzenesulfonamides.[19] This alternative is not common, but the alkylation of sulfonamide linker **81** is given in Scheme 19 as an example. In addition, intermediate **82** can be used for the synthesis of *N*-alkyl hydroxamic acids.[54]

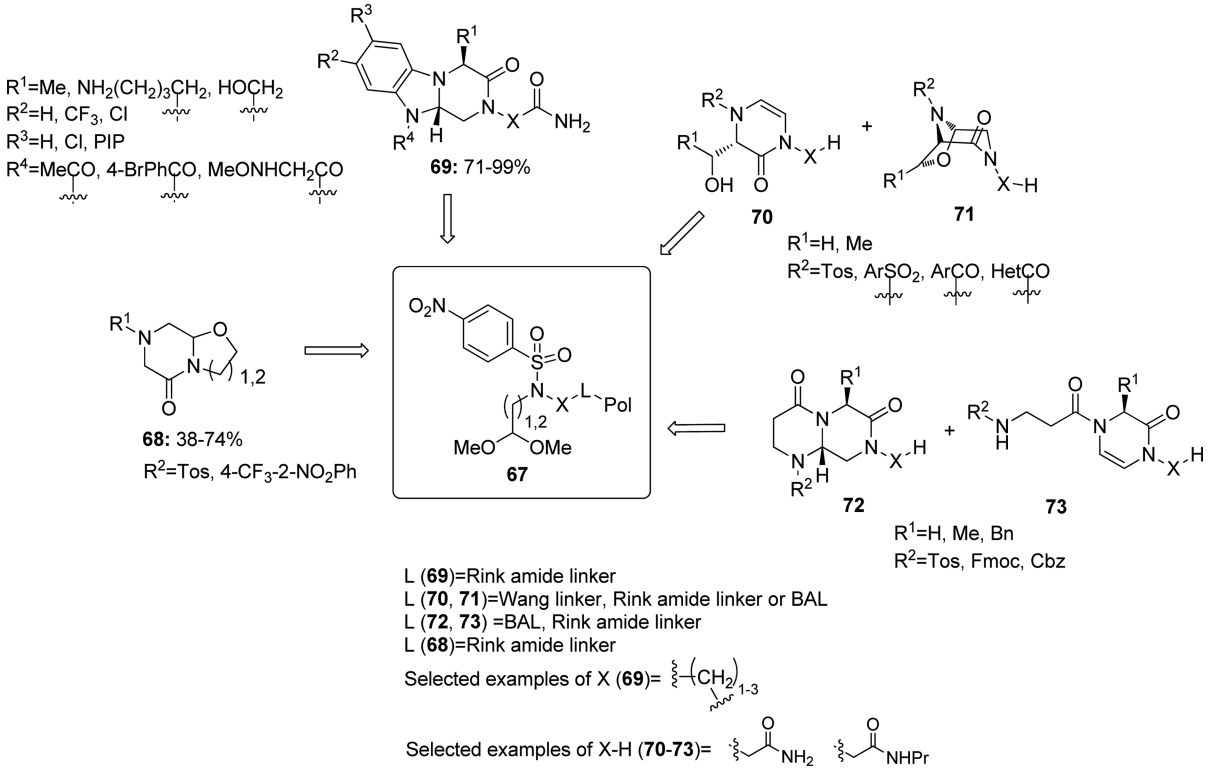
Methylation of immobilized Nos-amino acids with diazomethane in DCM (Scheme 20) was reported by Di Gioia et al.[67] The strategy enables simple and fast modification of amino acids with variable subtitution on a side chain.

2. SCENARIO B: COMBINED FUNCTION OF THE NOS GROUP

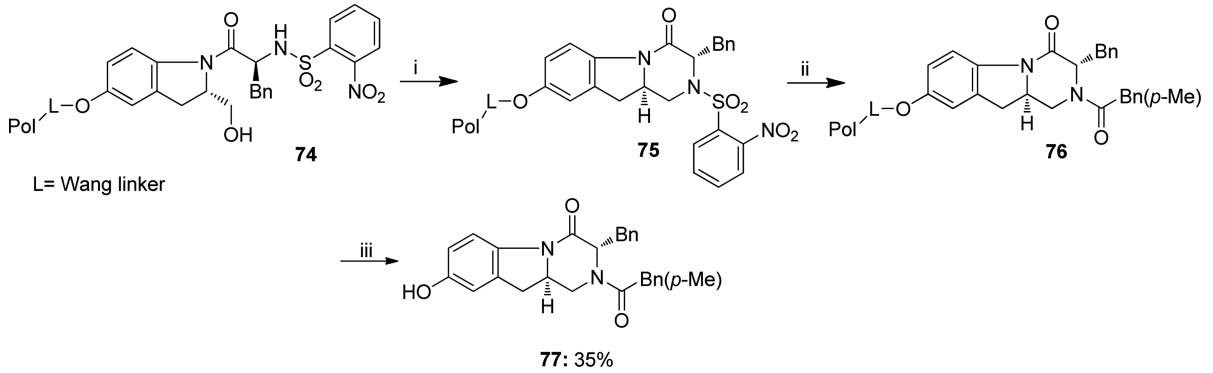
In the previous chapter, we summarized different strategies in which the Nos group was applied only as a standard activating/protecting group. Accordingly, the Nos group was cleaved after alkylation. Numerous examples also exist that omit this cleavage. Furthermore, certain reactions are triggered by bases that do not cleave the Nos group but result in intramolecular C/N-arylations. In both cases, the Nos group was used as the activating/protecting group for alkylation, but the benzenesulfonamide moiety (or at

DOI: 10.1021/acscombsci.5b00089
ACS Comb. Sci. 2015, 17, 570−591

Scheme 16. Examples of Various Heterocyclic Scaffolds Synthesized via Acetal Intermediates 67

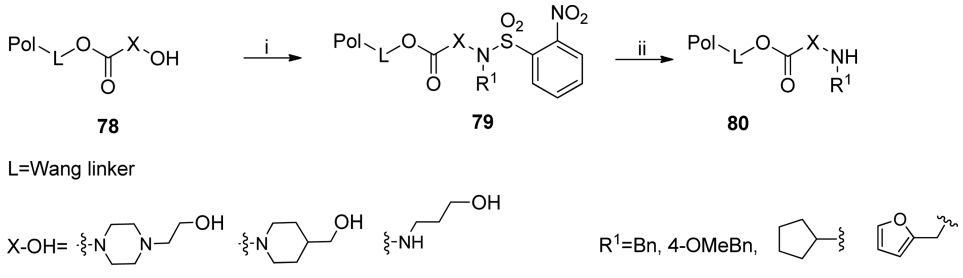


Scheme 17. Intramolecular Cyclization under Fukuyama–Mitsunobu Conditions[a]



[a]Reagents: (i) DEAD, Ph_3P, THF; (ii) (a) PhSH, DBU, DMF, (b) HOBt, DIC, Bn-(*p*-Me)-COOH, DMF; (iii) 10% TFA in DCM.

Scheme 18. Reversed Mitsunobu Alkylation of Nitrobenzenesulfonamides[a]



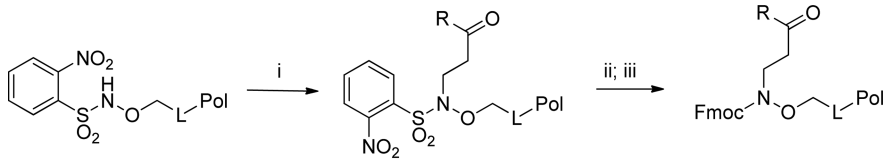
[a]Reagents: (i) 2-Nos-NHR[1], PPh_3, di-*tert*-butylazodicarboxylate (DTAD), DCM/THF (1:1); (ii) 2-mercaptoethanol, DBU, DMF.

least its aromatic portion in the case of C/N arylations) was preserved in the final molecule.

2.1. Preservation of the Nos Group To Give Linear Nitrobenzenesulfonamides. The term "linear nitrobenzenesulfonamides" refers to compounds in which the sulfonyl group is not included in the cyclic moiety. There are three general reasons why the Nos group is preserved in the final product structure after Fukuyama or Fukuyama–Mitsunobu alkylation: (i) the

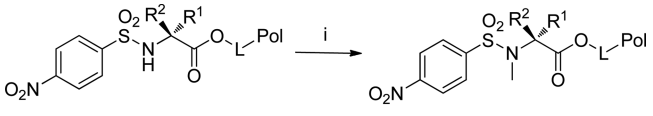
DOI: 10.1021/acscombsci.5b00089
ACS Comb. Sci. 2015, 17, 570–591

Scheme 19. Synthesis of *N*-Alkylamines with Unsaturated Ketones[a]



[a]Reagents: (i) α,β-unsaturated ketone, 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2 diazaphosphorine (BEMP), anhydrous THF; (ii) 2-mercaptoethanol, DBU, DMF; (iii) 9-Fluorenylmethyl *N*-succinimidyl carbonate (Fmoc-OSu), DCM.

Scheme 20. Synthesis of *N*-Methyl Amino Acids with Diazomethane[a]



R^1 = Me, i-Pr, CH_2S-CH_2Ph, CH_2O-(t-Bu), $(CH_2)_4NH$-(Boc) etc.
R^2 = H, Bn

[a]Reagents: (i) CH_2N_2, DCM.

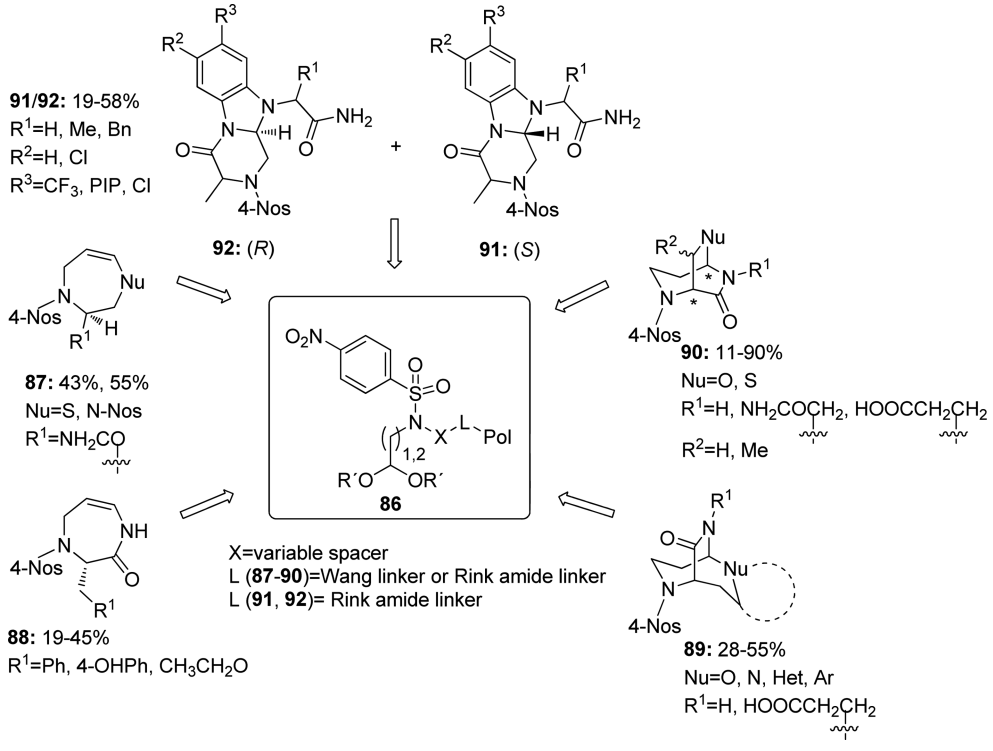
nitrobenzenesulfonamide scaffold can serve as a chromophore to enable simple HPLC−UV detection of UV−vis-inactive intermediates; (ii) it can increase the structural diversity of the synthesized molecules; and (iii) it can provide a reactive internal nucleophile.

One of the frequent methods leading to linear benzenesulfonamides is iminium chemistry, as mentioned in subchapter 1.2. Scheme 21 outlines the preparation of different heterocycles via masked aldehyde **86** as the key intermediate.[68,69] In each case, the nitrobenzenesulfonamide scaffold remained in the final structure.

Ketone groups in acyclic precursors can also be used to produce *N*-alkyliminium intermediates, as in the synthesis of trisubstituted tetrahydropyrazines and piperazines (Scheme 22).[70] First, the *N*-Nos-protected terminal amino group of intermediate **93** was alkylated with a bromoketone. Subsequent treatment of intermediate **94** with 50% TFA yielded the target tetrahydropyrazine **95**. Advantageously, addition of the reducing agent triethylsilane (TES) into the cleavage cocktail formed the corresponding piperazine derivatives **96**.

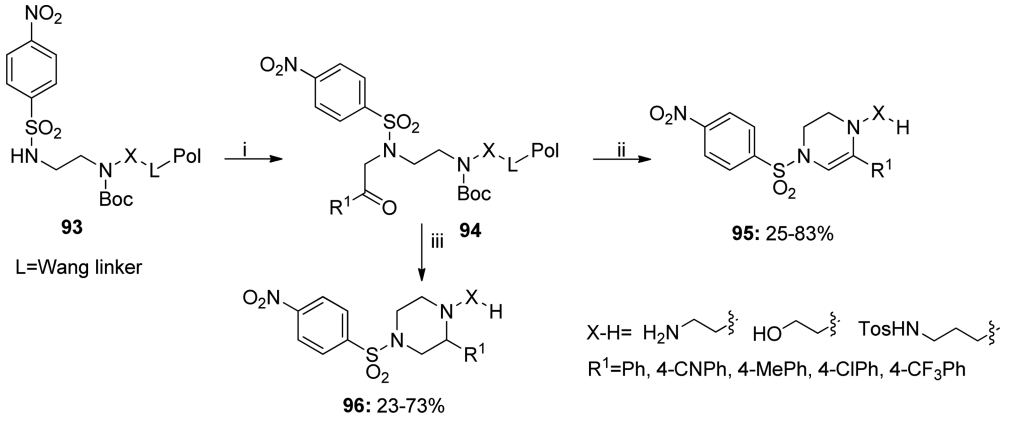
Intramolecular azomethine ylide cycloaddition has also been used to produce nitrogenated Nos heterocycles in the stereoselective synthesis of polycyclic compounds.[71] Immobilized α-*N*-Boc-β-*N*-Nos-diaminopropionic acid served as a starting material for the construction of α-*N*-imine and β-*N*-Nos-olefin residues **97** (Scheme 23). Subsequent application of a suitable catalytic system triggered formation of the ylide to yield bicyclic pyrrolidines **98**. Nosylated bicycles were either cleaved from the polymer support (compound **99**) or further modified to afford tricyclic triazacyclopenta[*c*]pentalene **101**.

Scheme 21. Examples of Linear Sulfonamides Synthesized via a Masked Aldehyde Intermediate



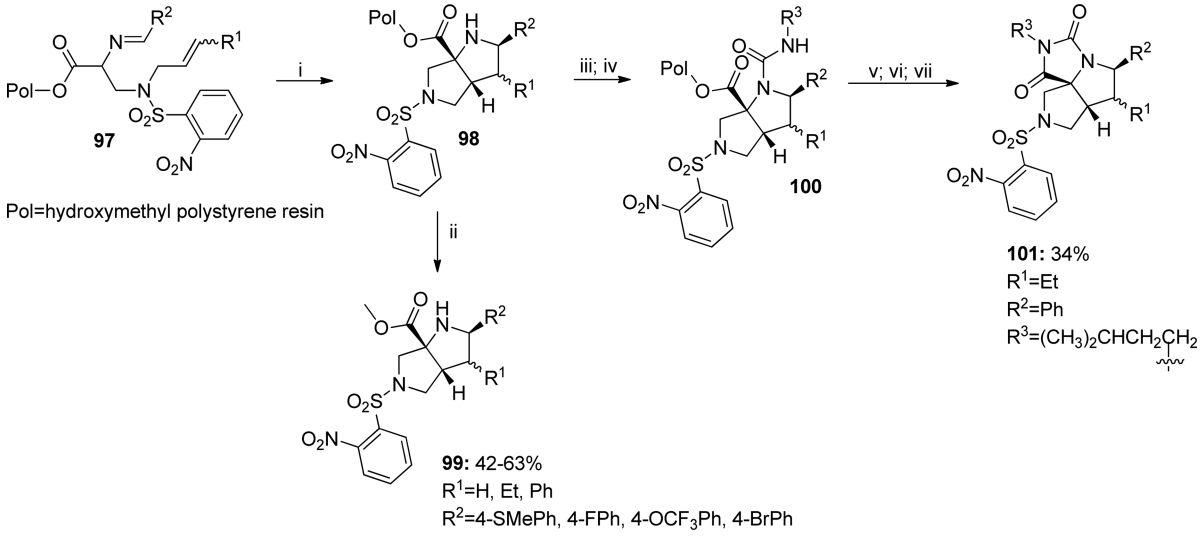
DOI: 10.1021/acscombsci.5b00089
ACS Comb. Sci. 2015, 17, 570−591

Scheme 22. Synthesis of Piperazines and Tetrahydropyrazines via a Ketone-Containing Acyclic Precursor[a]



[a]Reagents: (i) bromoketone, DIEA, DMF; (ii) 50% TFA in DCM; (iii) 10% TES, 50% TFA, 40% DCM.

Scheme 23. Synthesis of Polycyclic Compounds via the Azomethine Ylide Transition State[a]



[a]Reagents: (i) $Zn(OAc)_2$, DBU, anhydrous MeCN; (ii) MeOH, KOH; (iii) phosgene, DIEA, DCM; (iv) R^3NH_2, DCM; (v) PhSNa, DMF; (vi) re-nosylation: 2-Nos-Cl, TEA, DCM (reductive alkylation or acylation is also possible); (vii) ^{t}BuOK, THF.

Olsen et al.[72] described the first example of aminolysis of *N*-Nos-activated/protected aziridine-2-carboxylic acids on resin (Scheme 24). Starting aziridines **102** were exposed to different amines with terminal hydroxy or amino groups, and the final ring closure of intermediate **103** was accomplished under Mitsunobu conditions or with 1,1′-thiocarbonyldiimidazole ($CSIm_2$) to yield enantiomerically pure heterocycles **104** and **105**.

In 2006, Stanger and Krchňák[30] developed an efficient procedure for the synthesis of both *N*-H and *N*-R hydroxamates from O-linked hydroxylamines **106** (Scheme 25), which was later used to prepare a small library of *β*-sulfonamide hydroxamates **108**. These were tested for inhibition of breast cancer cell proliferation,[73] and compound **109** was found to be the best inhibitor.

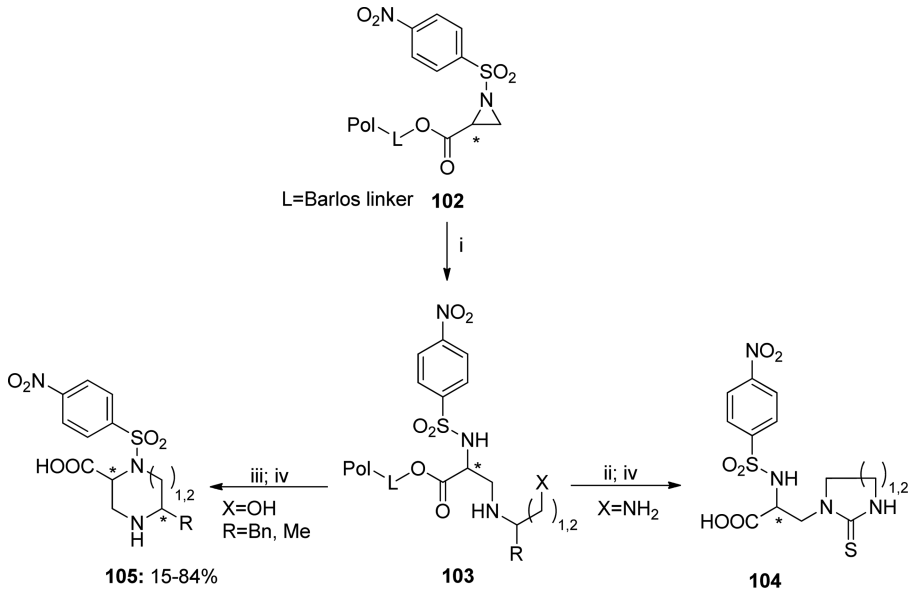
2.2. Incorporation of the 2-Nos Group Resulting in Cyclic Sulfonamides. This alternative has been typically applied with 2-nitrobenzenesulfonamides. When the nitro group of suitable intermediates is reduced, the intramolecular cyclization reaction yields the cyclic benzenesulfonamides. A typical example is the preparation of tetrahydrobenzopyrazinothiadiazinone dioxides **113** (Scheme 26).[74] 4-Nos-Cl was primarily used to synthesize the masked aldehyde precursor **67**, whereas substituted 2-Nos-Cls were subsequently applied as synthons to produce intermediates **113**. After reduction of the nitro group, the target compounds **113** were obtained via the corresponding *N*-sulfonyliminium intermediates.

In the same year, the synthesis of dihydrobenzothiadiazepine 1,1-dioxides **118** was published (Scheme 27).[75] First, the immobilized sulfonamide **114** was alkylated with various bromoketones. After reduction of the nitro group, cleavage from the polymer support yielded mixtures of compounds **117** and **118** in variable ratios. Further NMR investigation of the mixtures demonstrated that linear sulfonamides **117** spontaneously cyclized in deuterated dimethyl sulfoxide (DMSO-d_6). The cyclization time was remarkably accelerated for compounds bearing a methoxy group at position R^2.

Subsequent experiments (LC/MS, 1D NMR) revealed that dihydrobenzothiadiazepine 1,1-dioxides **118** (Scheme 27) are not stable in DMSO-d_6 at room temperature, and 2D NMR spectroscopy confirmed an unprecedented ring contraction yielding 4*H*-benzo[*b*][1,4]thiazine 1,1-dioxides **119** (Scheme 28).[76] Target compounds **120** are not cyclic benzenesulfonamides, but the rearrangement is included here to show the synthetic possibilities of the nitrobenzenesulfonamide chemistry.

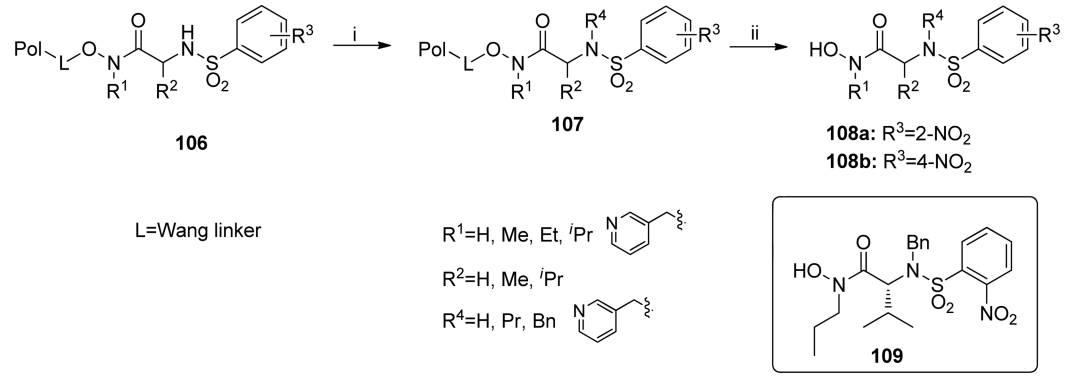
DOI: 10.1021/acscombsci.5b00089
ACS Comb. Sci. 2015, 17, 570−591

Scheme 24. Aminolysis of Resin-Bound Aziridines To Synthesize Enantiopure Heterocycles[a]



[a]Reagents: (i) diamine or amino alcohol, THF; (ii) $CSIm_2$, DCM; (iii) DEAD, PEt_3 or ADDP, PMe_3; (iv) TFA, DCM.

Scheme 25. Synthesis of *N*-Alkyl Hydroxamates[a]



[a]Reagents: (i) benzyl or primary alcohol, PPh_3, DIAD, anhydrous THF; (ii) TFA, DCM.

2.3. Application of the Nos Group for Fukuyama Alkylation Followed by C/N-Arylation. Seven years ago, a striking difference in the reactivity of 2-nitrobenzenesulfonamides and 4-nitrobenzenesulfonamides was observed. Treatment of 4-Nos derivatives **121** with mercaptoethanol and DBU afforded the standard deprotected products **122**, whereas cleavage of 2-Nos derivatives **123** caused the C-arylation followed by release of sulfur dioxide to afford **125**, which spontaneously cyclized to give indazole oxide derivatives **126** (Scheme 29).[24] Rearrangement was enabled by the acidic methylene group hyperconjugated with the carbonyl functionality originating from the alkylating agents such as bromoketones, bromoacetates, benzyl alcohols, or pyridylmethanols. The electron-withdrawing groups in aryl building blocks at position R^2 facilitated C-arylation to give benzhydrylamine derivatives **127**.[77]

Application of this tandem C−C and N−N rearrangement has been widely used to give diverse scaffolds. Depending on the reaction conditions, type of base, substitution pattern, and structure of the individual linkers, C-arylated intermediates **128** were converted into various indazole oxides and iminium salts suitable for other chemical transformations (Scheme 30).[24,25,77−80]

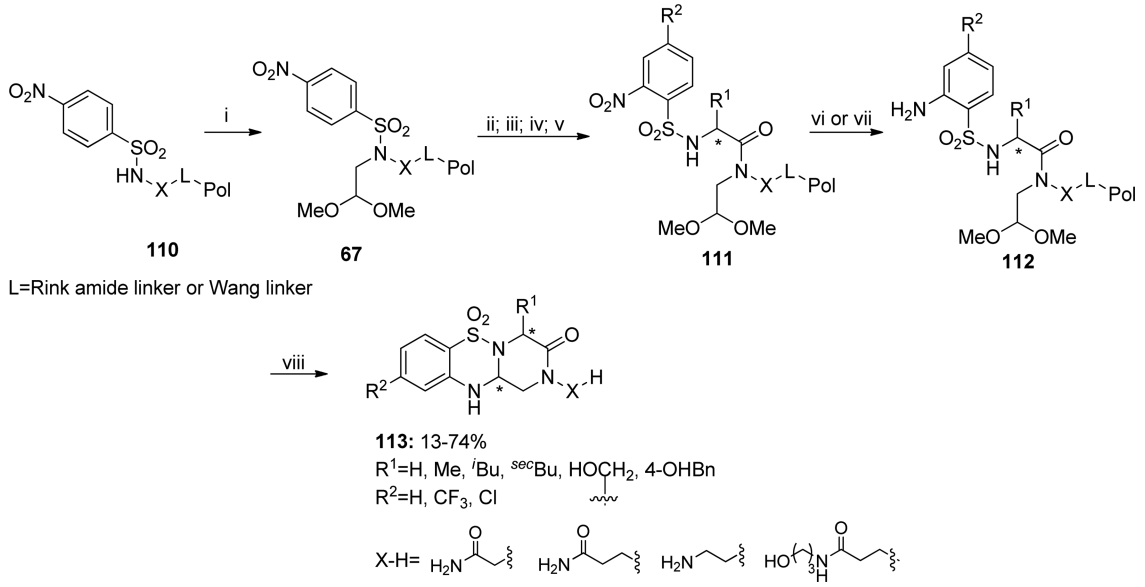
To access the parent 2*H*-indazoles, several methods for the reduction of indazole oxides have been evaluated, with mesyl chloride and TEA being the most efficient reagents.[81] This procedure was used for the traceless synthesis of 3,4-dihydropyrazino[1,2-*b*]indazoles (Scheme 31).[26] The immobilized and deoxygenated product **138** was treated with 50% TFA, which caused the release of the desired pyrazinoindazoles **139**. In contrast, performing the cyclization with TEA in MeOH yielded the final derivatives **141** when a carboxylate substituent was at the R^3 position.

Attempts to expand the scope of indazole oxide transformations led to the discovery of a novel ring expansion (Scheme 32).[82] A proposed mechanism for this reaction consisted of base-mediated compensation for the electron deficit on the nitrogen of the *N*-oxide group (**143**). After scission of the N−N bond, subsequent rearrangement of intermediates **144** provided the quinazoline derivatives **145**. 4-Arylquinazolines **147** were obtained in the same manner.[77]

In addition to different indazole or quinazoline derivatives, C-aryl intermediates were applied in the preparation of trisubstituted 1*H*-indoles.[25] Addition of a base to the acyclic intermediate **124** induced the C-arylation, yielding the

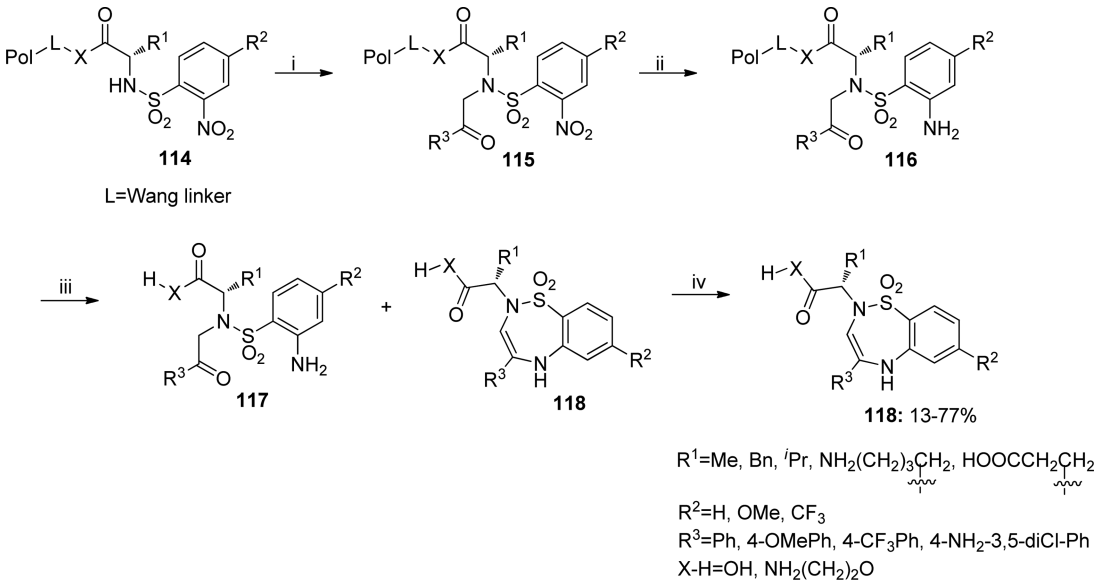
DOI: 10.1021/acscombsci.5b00089
ACS Comb. Sci. 2015, 17, 570−591

Scheme 26. Synthesis of Cyclic Sulfonamides by *N*-Sulfonyliminium Chemistry[a]



[a]Reagents: (i) glycolaldehyde dimethyl acetal, PPh_3, DIAD, anhydrous THF, 0−50 °C; (ii) 2-mercaptoethanol, DBU, DMF; (iii) Fmoc-α-AA-OH, HOBt, DIC, DCM/DMF (1:1); (iv) 50% piperidine in DMF; (v) 2-Nos-Cl, 2,6-lutidine, DCM; (vi) $SnCl_2{\cdot}2H_2O$, DIEA, DMF (saturated with N_2), 50 °C; (vii) $Na_2S_2O_4$, tetrabutylammonium hydrogen sulfate (TBAHS), K_2CO_3, DCM/H_2O (1:1); (viii) 50% TFA in DCM.

Scheme 27. Synthesis of Dihydrobenzothiadiazepine 1,1-Dioxides[a]



[a]Reagents: (i) bromoketone, DIEA, DMF; (ii) $Na_2S_2O_4$, K_2CO_3, TBAHS, DCM/H_2O (1:1); (iii) 50% TFA in DCM; (iv) DMSO-d_6.

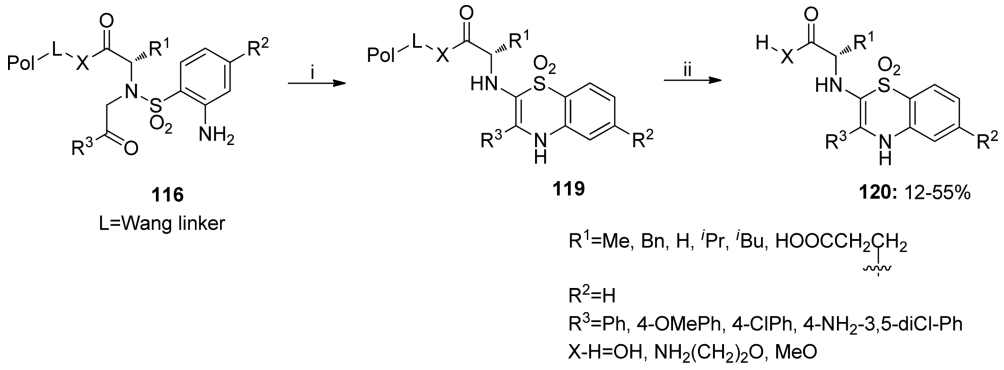
compound **148** (Scheme 33). After reduction of the nitro group, an unprompted cyclization afforded 1*H*-indoles **149**. The final compounds **150** were obtained after cleavage from the polymer support. Nevertheless, in the case of linkers **124e−g**, it was necessary to protect the amino group of C-arylated precursors **148** to avoid undesirable indazole oxide formation.

The effects of different linkers, amino acids, and benzyl alcohols on C-aryl formation were evaluated to determine the scope and limitations of these reactions.[26] Surprisingly, DBU-mediated arylation of compound **153** containing alanine anchored to an ester-based linker and a 2-NO_2Ph group at the R^2 position afforded a mixture of benzylic sp^3-arylated (**154a**) and α-C-arylated (**155a**) compounds (Scheme 34). However, introduction of more bulky amino acids resulted in direct sp^3 arylation and creation of the expected products **154a** mostly in excellent purity. The assessed piperazine linker resulted in either benzylic sp^3-arylated (**154b**) or α-C-arylated (**155b**) compounds according to the building blocks and reaction conditions used. Secondary-amide-based dual substrates were also evaluated in this context. Unexpectedly, the DBU-mediated reaction did not afford α-C-arylation but rather gave N-arylated compound **156** (for the proposed reaction mechanism, see Scheme 35). The benzylic sp^3 product **154c** could also be prepared depending on the substitution of the benzyl ring.

C/N-Arylation has been observed previously in both the solution phase[83−85] and the solid phase. Bienz and co-workers[86]

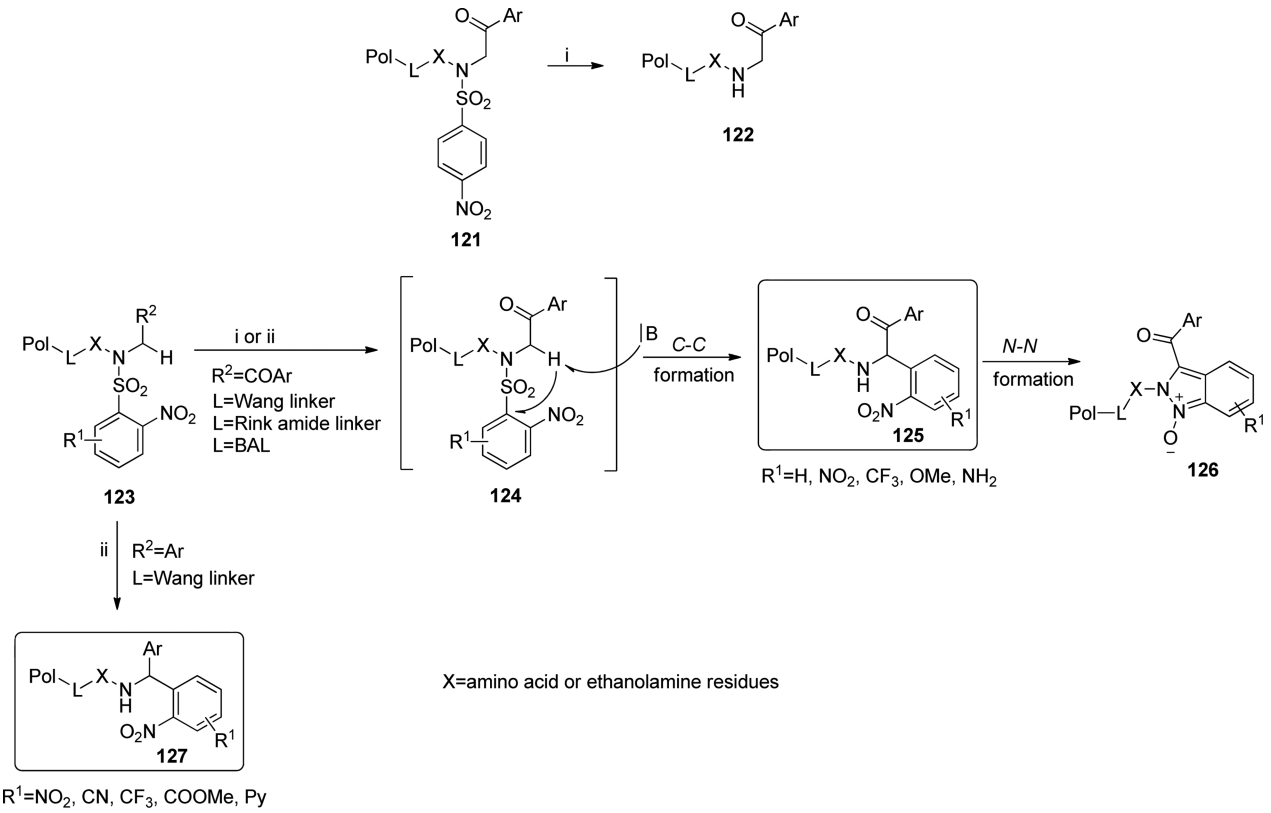
DOI: 10.1021/acscombsci.5b00089
ACS Comb. Sci. 2015, 17, 570−591

Scheme 28. Synthesis of Thiazine Dioxides via Ring Contraction of Thiadiazepine Dioxides[a]



[a]Reagents: (i) 5% AcOH in DMSO, 80 °C; (ii) 50% TFA in DCM.

Scheme 29. Different Reactivities of 2-Nos and 4-Nos Derivatives toward DBU[a]



[a]Reagents: (i) 2-mercaptoethanol, DBU, DMF; (ii) DBU, DMF.

developed methodology leading to cyclic polyamines. One of the proposed synthetic routes utilized 2,4-dinitrobenzenesulfonyl chloride as an alternative to 2-Nos-Cl in the subsequent Mitsunobu reaction (Scheme 36). However, after cleavage of **158** from the polymer support followed by methanolysis, N-arylated compounds **160** and **161** were obtained instead of the desired product **159**. Attempts to release the 2,4-dinitrobenzenesulfonyl group prior to cleavage from the resin led to the major compound **160**.

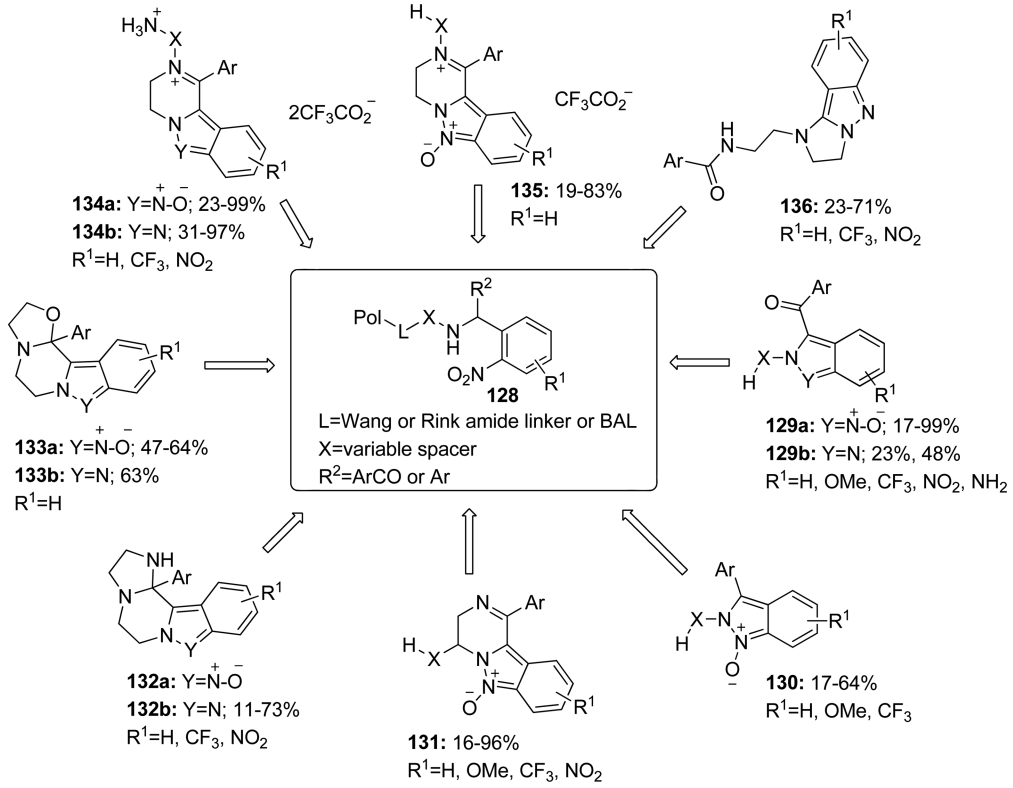
3. SCENARIO C: NOS GROUP USED EXCLUSIVELY AS A SYNTHON

The applications of polymer-supported nitrobenzenesulfonamides in Fukuyama or Fukuyama–Mitsunobu alkylation were summarized in the previous chapters. These applications are the most common, but 2-Nos-Cl and 4-Nos-Cl have also been applied as common building blocks without alkylation of the corresponding sulfonamides. In such cases, the benzenesulfonamide moiety is either integrated into the target scaffold to access reactive intermediates for further derivatization or, because of skeletal similarity of target compounds, to synthesize biologically active molecules.

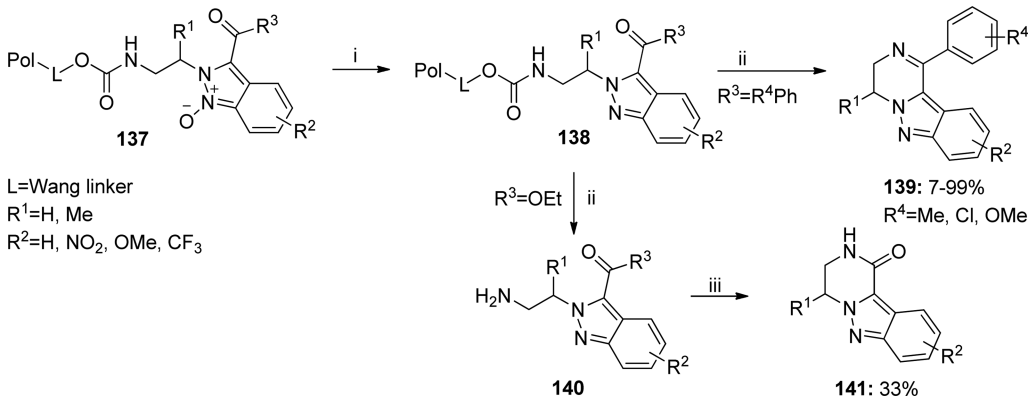
In 1998, Richter and Jung[87] developed the first version of the Baylis–Hillman reaction in the solid phase (Scheme 37). The one-pot procedure was based on the reaction of immobilized olefin **162** with aldehyde **163** and 4-nitrobenzenesulfonamide **164** catalyzed by DABCO. The final cleavage of the resulting compounds **165** from the polymer support was accomplished using TFA in DCM.

DOI: 10.1021/acscombsci.5b00089
ACS Comb. Sci. 2015, 17, 570–591

Scheme 30. Examples of Diverse Indazole-Based Heterocycles Generated from C-Arylated Precursors



Scheme 31. Traceless Synthesis of 3,4-Dihydropyrazino[1,2-*b*]indazoles[a]



[a]Reagents: (i) methanesulfonyl chloride, TEA, DCM; (ii) 50% TFA in DCM; (iii) TEA, MeOH.

Four years later, another one-pot polymer-supported synthesis of α-sulfonylaminoamide derivatives was published.[88] This study targeted the scope and limitations of the Ugi condensation reaction (Scheme 38). The optimized conditions were compatible with carboxy polystyrene resin **167**, 2/4-nitrobenzenesulfonamides, and *tert*-butyl isocyanide, which provided the desired products **169** in high overall yields.

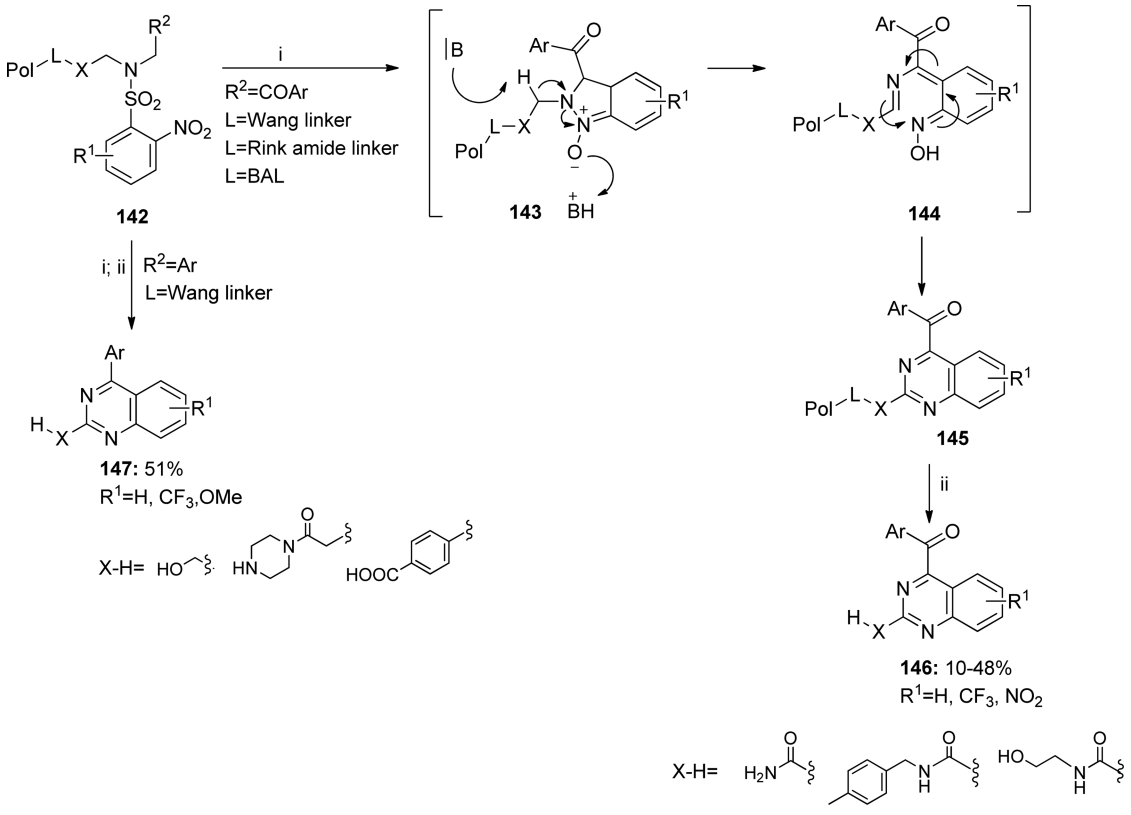
Gong and co-workers[29] synthesized *N*-hydroxypiperazine derivatives from phenethylpiperazine linker **170**, which was derivatized with 4-Nos-Cl. The corresponding 4-nitrophenylsulfonylpiperazine **171** was converted to *N*-oxide intermediate **172** through oxidation with *m*-chloroperoxybenzoic acid (Scheme 39). The final transformation leading to release of the product **173** from the polymer support was accomplished through a Cope β-elimination reaction.

Maclean et al.[89] used polymer-supported 4-nitrobenzenesulfonamide derivative **175** to construct a safety-catch linker. Previously, the original *S*-immobilized-*N*-acylsulfonamide (Kenner) linker[90] had been widely used in peptide synthesis, and several of its modifications have been reported, including the sulfonamide carbamate (reversed Kenner) linker. The nitro group of key intermediate **175** was reduced and subsequently used to prepare thiazolidinone products (Scheme 40). Depending on the cleavage conditions, different thiazolidinones **179** or their succinate analogues **180** were obtained.

Incorporation of the Nos group can also introduce analogues of biologically active compounds. A convenient solid-phase technique prepared simple arylsulfonamide molecules derived from putrescine.[91] Nucleophilic displacement of carbonate **192** by putrescine provided immobilized amine **193**, which was further exposed to Nos-Cls (Scheme 41). The desired

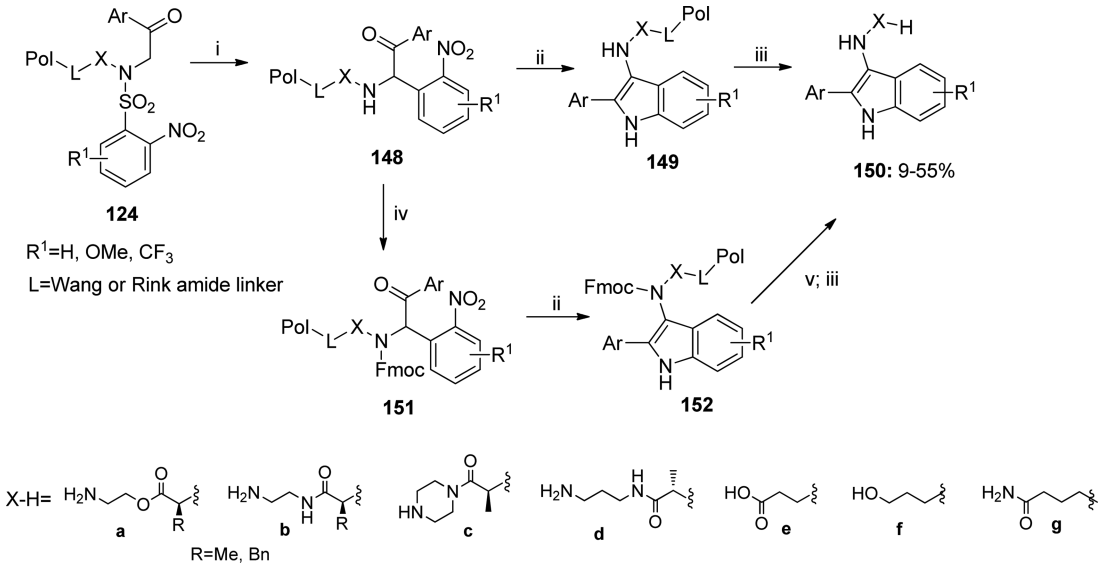
DOI: 10.1021/acscombsci.5b00089
ACS Comb. Sci. 2015, 17, 570−591

Scheme 32. Rearrangement of Indazole Oxides Leading to Quinazolines[a]



[a]Reagents: (i) DBU, DMF; (ii) 50% TFA in DCM.

Scheme 33. Synthesis of 2-Aryl-3-alkylamino-1*H*-indoles from C-Arylated Precursors[a]



[a]Reagents: (i) 1,4-diazabicyclo[2.2.2]octane (DABCO) or TEA, DMF; (ii) $Na_2S_2O_4$, K_2CO_3, TBAHS, H_2O/DCM (1:1); (iii) TFA/DCM (1:1) or TFA/TES/DCM (5:1:4) for Fmoc-protected compounds; (iv) Fmoc-Cl, DCM; (v) piperidine, DMF.

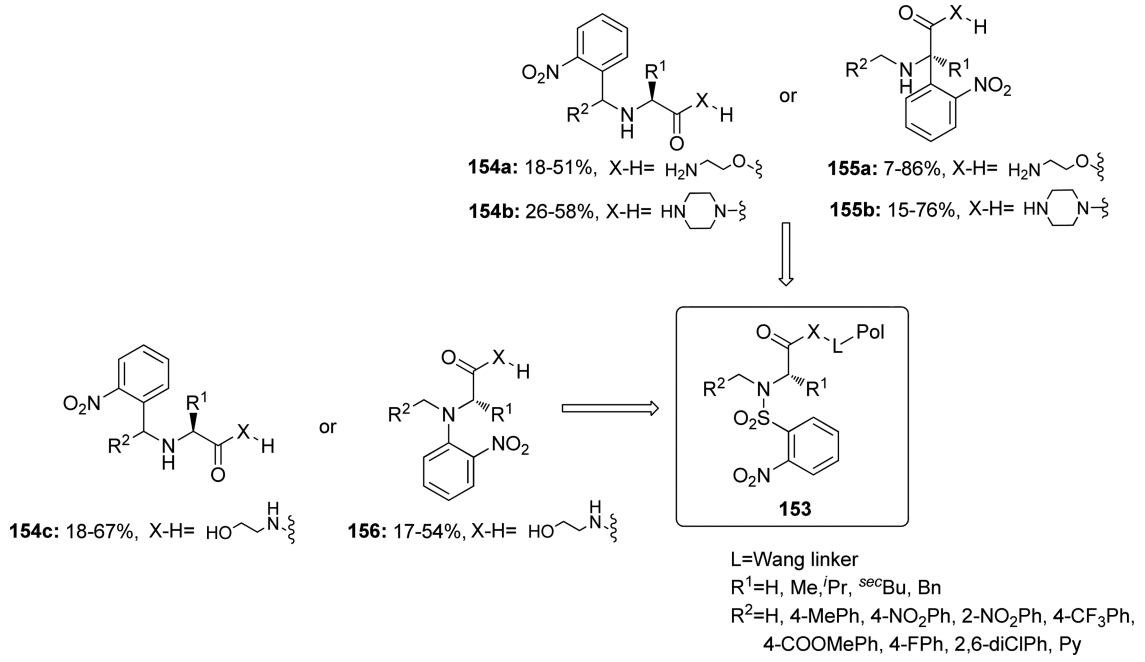
compounds **194** were prepared as potential ligands of serotonin 5-HT_6 receptors.

Nicolaou et al.[92] utilized the previously developed procedure in the split-and-pool synthesis of a large natural-product-like library based on the benzopyran scaffold (Scheme 42). The starting aldehyde **195** was immobilized onto a selenium resin via ring closure (intermediate **196**). Subsequent condensation and reductive amination yielded intermediate **197**. After reaction with Nos-Cl and final oxidative cleavage, the target scaffold **199** was obtained. Subsequent modification in the solution phase led to diverse sulfonamide products **200**.[93]

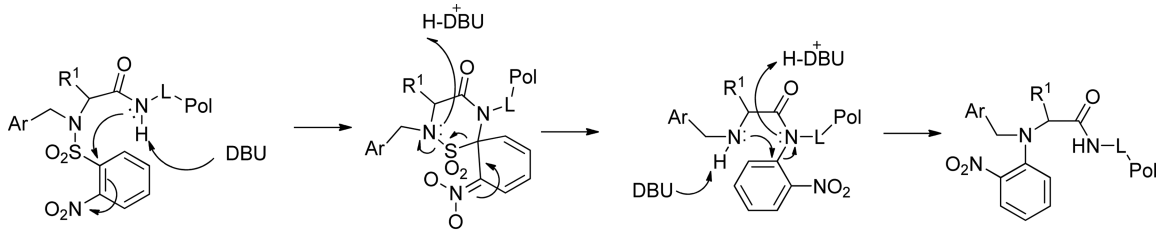
In 2002, a solid-phase method was used to synthesize 1,2,4-benzothiadiazin-3-one 1,1-dioxides on solid supports for the first time.[94] The synthesis is based on sulfonylation of anchored

DOI: 10.1021/acscombsci.5b00089
ACS Comb. Sci. 2015, 17, 570−591

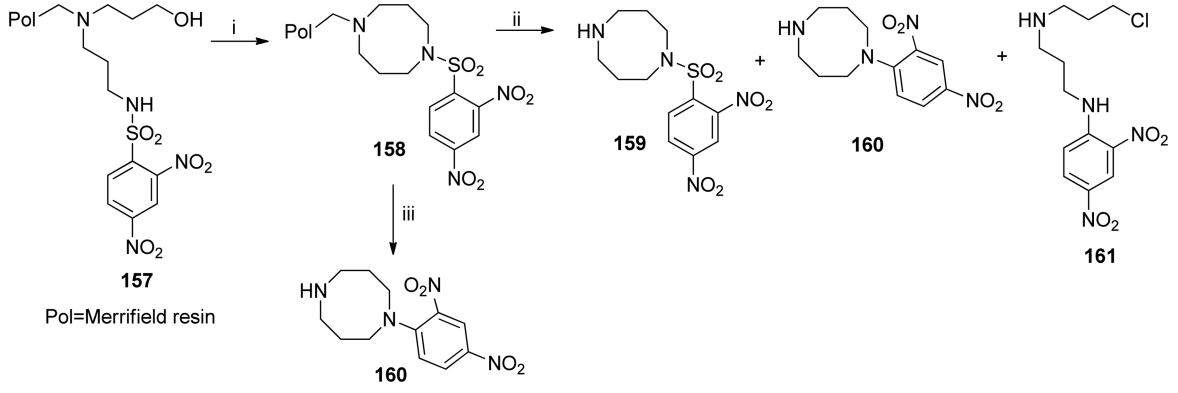
Scheme 34. Examples of DBU-Mediated α-C-Arylation and N-Arylation



Scheme 35. Proposed Mechanism for N-Arylation

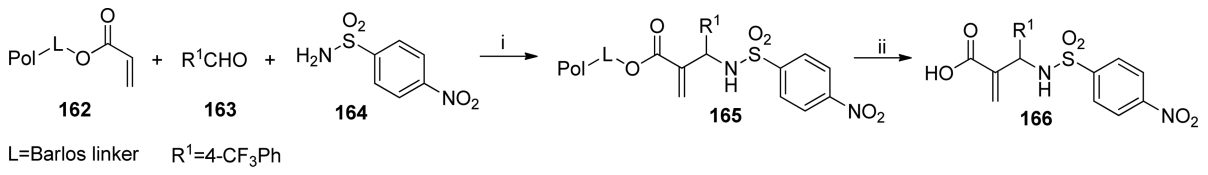


Scheme 36. Smile-Type Rearrangements in the Synthesis of Cyclic Amines[a]



[a]Reagents: (i) PPh_3, DEAD, anhydrous THF; (ii) (a) 1-chloroethyl chloroformate (ACE-Cl), dichloroethane (DCE), (b) MeOH, reflux; (iii) mercaptoacetic acid, DIEA or PhSH, K_2CO_3.

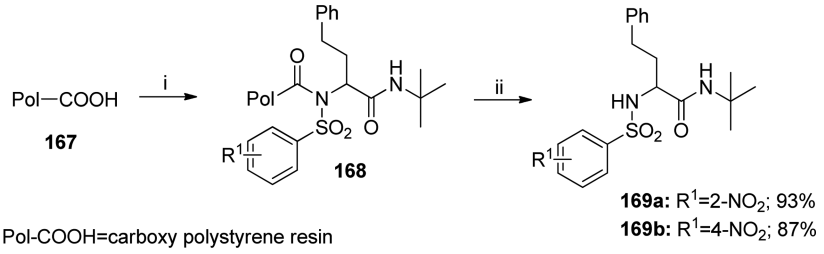
Scheme 37. One-Pot Baylis–Hillman Reaction on a Solid Support[a]



[a]Reagents: (i) DABCO, dioxane, 70 °C; (ii) TFA/DCM (5:95).

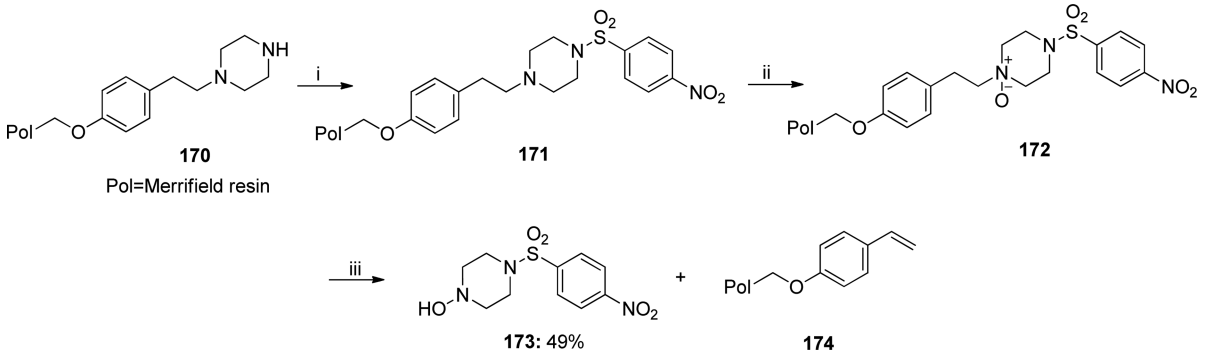
DOI: 10.1021/acscombsci.5b00089
ACS Comb. Sci. 2015, 17, 570–591

Scheme 38. Ugi-Type Four-Component Condensation[a]



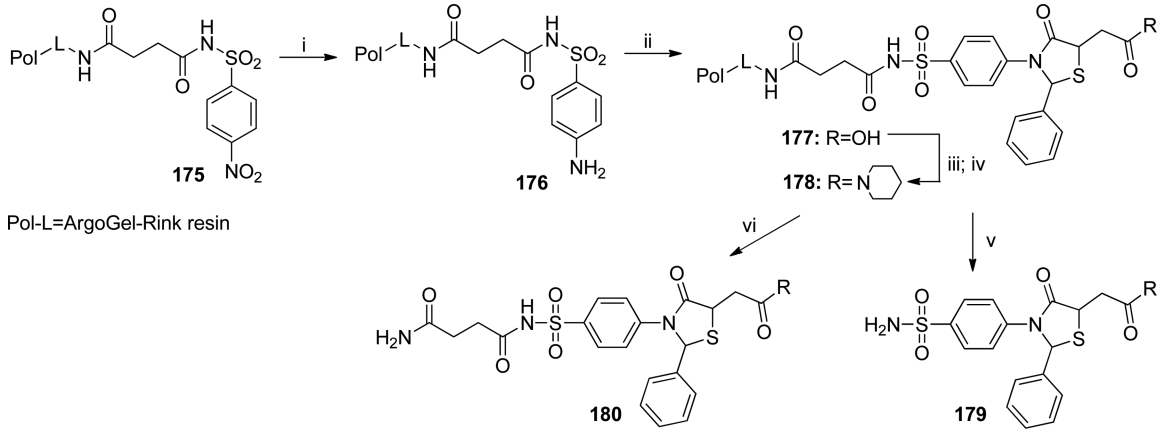
[a]Reagents: (i) hydrocinnamaldehyde, arylsulfonamide, *tert*-butyl isocyanide, THF, MeOH, 60 °C; (ii) 40% aqueous $MeNH_2$/THF (1:1 v/v).

Scheme 39. Synthesis of Hydroxypiperazine Derivatives via Oxidation−Cope Elimination[a]



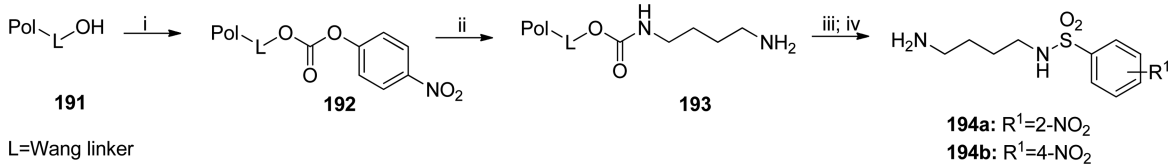
[a]Reagents: (i) 4-Nos-Cl, TEA, DMF; (ii) 3-chloroperoxybenzoic acid (*m*-CPBA), DCM; (iii) toluene, 90 °C.

Scheme 40. Synthesis of *N*-Alkylsulfonamides via "Reversed Kenner" Linkers[a]



[a]Reagents: (i) $SnCl_2$, DMF; (ii) PhCHO, mercaptosuccinic acid, 4 Å molecular sieves, THF, 70 °C; (iii) pentafluorophenyl trifluoroacetate/Py/DMF (1:1:1); (iv) 20% piperidine in DMF; (v) NH_3, MeOH; (vi) 50% TFA in DCM.

Scheme 41. Synthesis of Sulfonamide Ligands of 5-HT_6 Receptors[a]



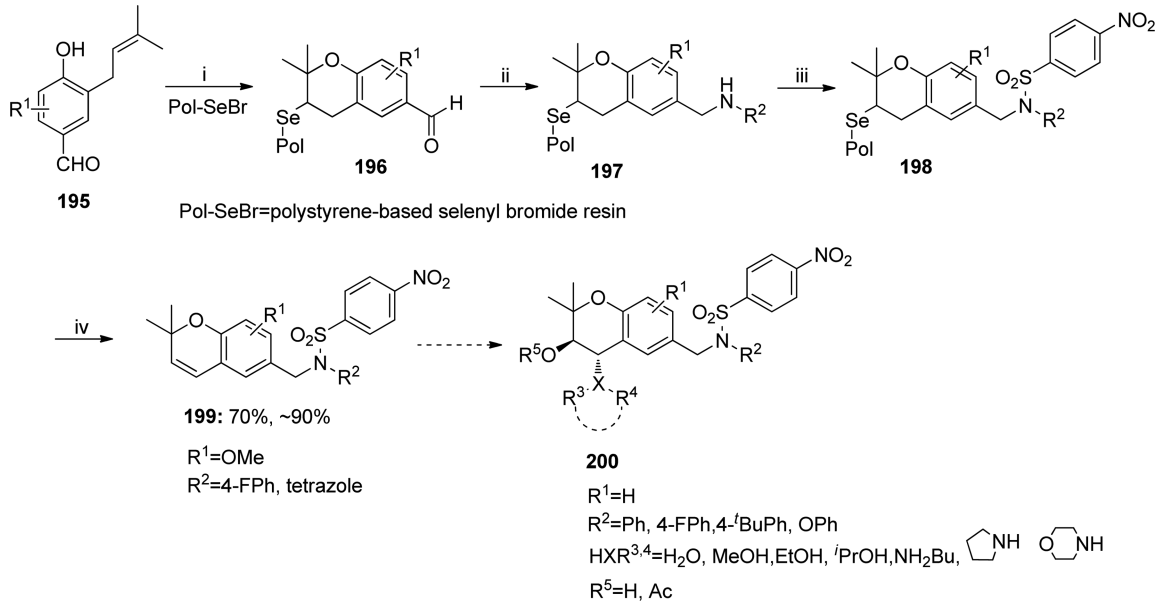
[a]Reagents: (i) 4-nitrophenyl chloroformate, NMM, DCM; (ii) putrescine, DCM; (iii) Nos-Cl, NMM, DCM; (iv) 50% TFA in DCM.

4-aminophenylacetamide **201** (Scheme 43). After reduction of an appropriate nitro group, the key cyclization was effortlessly achieved by the reaction of compound **203** with carbonyldiimidazole (CDI). To increase the diversity, compound **204** was treated with various alkyl halides, yielding products **205**.

The most recent contribution involves the solid-phase synthesis of anagrelide sulfonyl analogues.[95] The simple procedure was based on the immobilization of various natural amino acids that were treated with 2-Nos-Cl (Scheme 44). Reduction of the nitro group of compounds **206** followed by

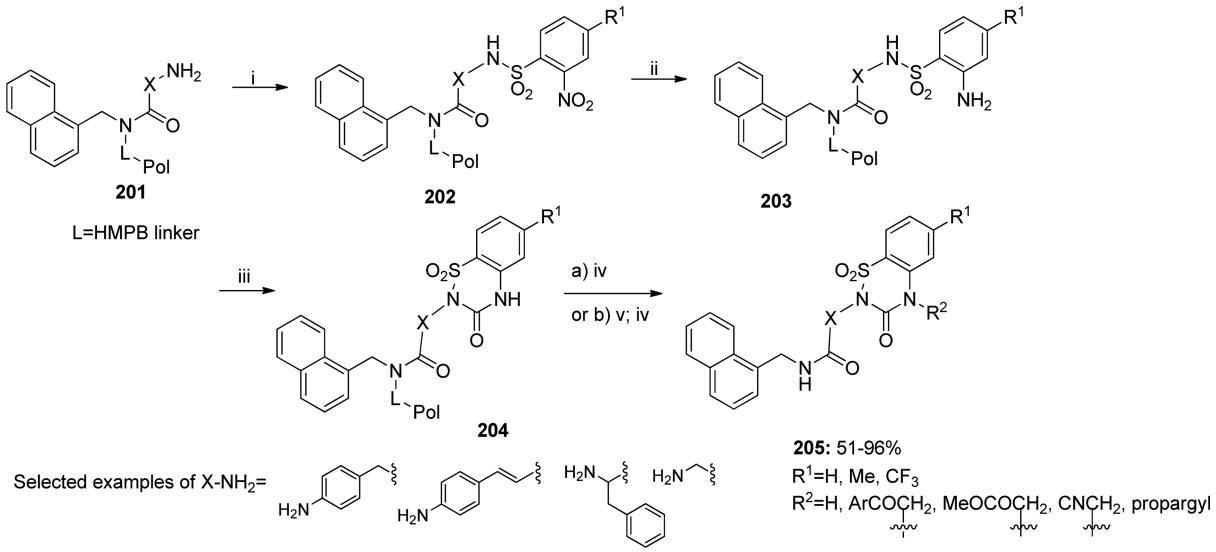
DOI: 10.1021/acscombsci.5b00089
ACS Comb. Sci. 2015, 17, 570−591

Scheme 42. Synthesis of Benzopyran Derivatives by Nicolaou[a]



[a]Reagents: (i) DCM; (ii) (a) R^2NH_2, THF, 65 °C, (b) $NaCNBH_3$, THF/MeOH (10:1), 65 °C; (iii) 4-Nos-Cl, TEA, 4-(*N*,*N*-dimethylamino)pyridine (DMAP), DCM; (iv) H_2O_2, THF.

Scheme 43. Synthesis of 1,2,4-Benzothiadiazin-3-one 1,1-Dioxides[a]



[a]Reagents: (i) 4-R^1-2-Nos-Cl, 2,6-di-*tert*-butyl-4-methylpyridine, DCM; (ii) $SnCl_2 \cdot 2H_2O$, NMP, EtOH; (iii) CDI, DCM; (iv) 95% TFA in H_2O; (v) R^2X, DIEA, NMP.

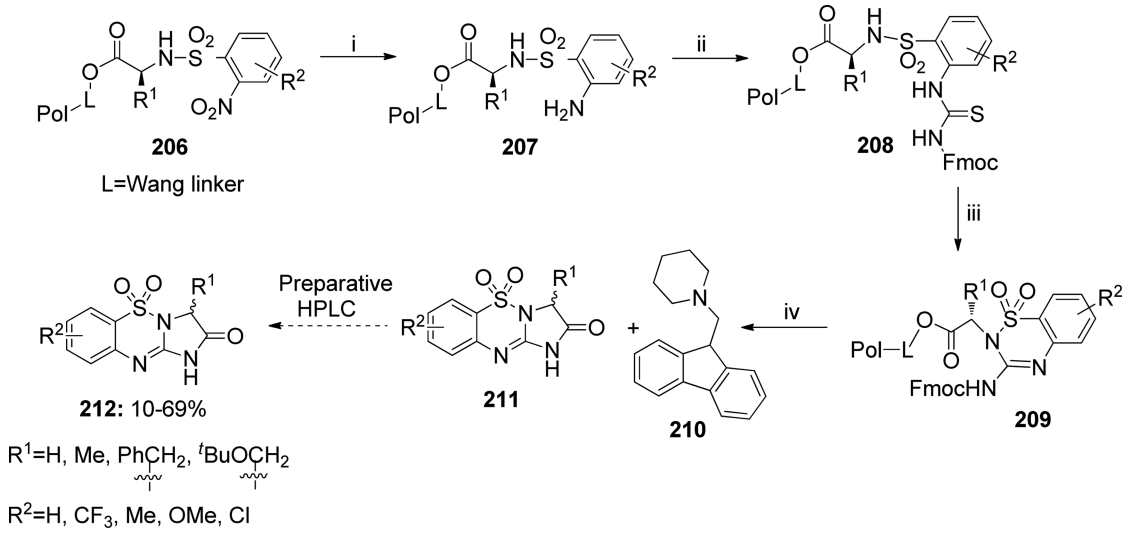
exposure to Fmoc-isothiocyanate (Fmoc-NCS) provided Fmoc-thiourea intermediates **208**. After DIC-triggered ring closure, final deprotection of the Fmoc group was followed by spontaneous cyclative cleavage to afford the target products **211**.

CONCLUSION

Polymer-supported nitrobenzenesulfonamides prepared from 2/4-Nos-Cl represent an important class of multifunctional intermediates in the production of either more or less complex compounds. In addition to the standard or modified Fukuyama alkylation protocol, the Nos group can be introduced into structures as a synthon. In such cases, interesting chemical transformations of 2-Nos intermediates have led to unprecedented rearrangements that have yielded novel derivatives of pharmacologically relevant heterocycles. Apart from planar scaffolds, compounds with 3D architecture (the presence of sp^3 carbons) and derivatives with stereoselective formation of new stereogenic centers are also accessible. With respect to complexity and high diversity, the use of immobilized nitrobenzenesulfonamides in connection with combinatorial SPS[96] represents an effective tool for the rapid preparation of numerous privileged heterocyclic scaffolds to cover a considerable part of the chemical space. In view of the increasing frequency of reported results, it is expected that this area will be significantly expanded in the near future.

DOI: 10.1021/acscombsci.5b00089
ACS Comb. Sci. 2015, 17, 570−591

Scheme 44. Synthesis of Anagrelide Sulfonyl Analogues[a]



[a]Reagents: (i) $Na_2S_2O_4$, K_2CO_3, TBAHS, DCM/H_2O (1:1); (ii) Fmoc-NCS, THF; (iii) DIC, DMF; (iv) piperidine, DMF.

AUTHOR INFORMATION

Corresponding Author

*Phone: +420 585634418, fax: +420 585634465 E-mail: soural@orgchem.upol.cz.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors are grateful to Project CZ.1.07/2.3.00/30.0060 from the European Social Fund and to Palacky University (Internal Grants IGA_PrF_2014018 and IGA_PrF_2015_007). The infrastructure of this project (Institute of Molecular and Translation Medicine) was supported by the National Program of Sustainability (Project LO1304).

REFERENCES

(1) Igwe, C. N.; Okoro, U. C. Synthesis, Characterization and Evaluation for Antibacterial and Antifungal Activities of *N*-Heteroaryl Substituted Benzene Sulphonamides. *Org. Chem. Int.* **2014**, *2014*, 419518.

(2) Ko, S. K.; Jin, H.; Jung, D. W.; Tian, X.; Shin, I. Cardiosulfa, a Small Molecule that Induces Abnormal Heart Development in Zebrafish, and Its Biological Implications. *Angew. Chem., Int. Ed.* **2009**, *48* (42), 7809–7812.

(3) Wani, M. Y.; Bhat, A. R.; Azam, A.; Choi, I.; Athar, F. Probing the Antiamoebic and Cytotoxicity Potency of Novel Tetrazole and Triazine Derivatives. *Eur. J. Med. Chem.* **2012**, *48* (0), 313–320.

(4) Gioiello, A.; Rosatelli, E.; Teofrasti, M.; Filipponi, P.; Pellicciari, R. Building a Sulfonamide Library by Eco-Friendly Flow Synthesis. *ACS Comb. Sci.* **2013**, *15* (5), 235–239.

(5) Giannotti, D.; Viti, G.; Sbraci, P.; Pestellini, V.; Volterra, G.; Borsini, F.; Lecci, A.; Meli, A.; Dapporto, P.; Paoli, P. New Dibenzothiadiazepine Derivatives with Antidepressant Activities. *J. Med. Chem.* **1991**, *34* (4), 1356–1362.

(6) Owa, T.; Yoshino, H.; Okauchi, T.; Yoshimatsu, K.; Ozawa, Y.; Sugi, N. H.; Nagasu, T.; Koyanagi, N.; Kitoh, K. Discovery of Novel Antitumor Sulfonamides Targeting G1 Phase of the Cell Cycle. *J. Med. Chem.* **1999**, *42* (19), 3789–3799.

(7) Ren, J.; Wang, Y.; Wang, J.; Lin, J.; Wei, K.; Huang, R. Synthesis and Antitumor Activity of *N*-Sulfonyl-3,7-dioxo-5*b*-cholan-24-amides, Ursodeoxycholic Acid Derivatives. *Steroids* **2013**, *78* (1), 53–58.

(8) Kim, D. H.; Yun, B. H.; Choi, E. W.; Oh, S. M.; Alam, M.; Lee, K. T.; Lee, Y. S. Synthesis and Cytotoxic Effects of Sulfonamide-Substituted 5,6,7-Trimethoxyflavones on Human Cancer Cell Lines. *Bull. Korean Chem. Soc.* **2013**, *34* (8), 2507–2510.

(9) Flosi, W. J.; DeGoey, D. A.; Grampovnik, D. J.; Chen, H. j.; Klein, L. L.; Dekhtyar, T.; Masse, S.; Marsh, K. C.; Mo, H. M.; Kempf, D. Discovery of Imidazolidine-2,4-dione-Linked HIV Protease Inhibitors with Activity Against Lopinavir-Resistant Mutant HIV. *Bioorg. Med. Chem.* **2006**, *14* (19), 6695–6712.

(10) Barea, C.; Pabón, A.; Castillo, D.; Zimic, M.; Quiliano, M.; Galiano, S.; Pérez-Silanes, S.; Monge, A.; Deharo, E.; Aldana, I. New Salicylamide and Sulfonamide Derivatives of Quinoxaline 1,4-di-*N*-Oxide with Antileishmanial and Antimalarial activities. *Bioorg. Med. Chem. Lett.* **2011**, *21* (15), 4498–4502.

(11) Samala, G.; Devi, P. B.; Nallangi, R.; Yogeeswari, P.; Sriram, D. Development of 3-Phenyl-4,5,6,7-tetrahydro-1*H*-pyrazolo[4,3-*c*]-pyridine Derivatives as Novel Mycobacterium Tuberculosis Pantothenate Synthetase Inhibitors. *Eur. J. Med. Chem.* **2013**, *69* (0), 356–364.

(12) 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* (36), 6373–6374.

(13) Kan, T.; Fukuyama, T. Ns Strategies: A Highly Versatile Synthetic Method for Amines. *Chem. Commun.* **2004**, *4*, 353–359.

(14) Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. Reductive Amination of Aldehydes and Ketones with Sodium Triacetoxyborohydride. Studies on Direct and Indirect Reductive Amination Procedures. *J. Org. Chem.* **1996**, *61* (11), 3849–3862.

(15) Pillai, R. B. C. Synthesis of Secondary Amines by Reductive Alkylation Using Copper Chromite Catalyst: Steric Effect of Carbonyl Compounds. *J. Mol. Catal.* **1993**, *84* (1), 125–129.

(16) Smith, M. B.; March, J. *March's Advanced Organic Chemistry*, 6th ed.; John Wiley & Sons: Hoboken, NJ, 2001.

(17) Mitsunobu, O. The Use of Diethyl Azodicarboxylate and Triphenylphosphine in Synthesis and Transformation of Natural Products. *Synthesis* **1981**, 1–28.

(18) Hughes, D. L. The Mitsunobu Reaction. *Org. React. (N. Y.)* **1992**, *42*, 335–656.

(19) Krchňák, V.; Slough, G. A. Polymer-Supported *N*-Benzyl- and *N*-Benzhydryl-2-nitrobenzenesulfonamides as Alternative to Aldehyde Linkers. *Tetrahedron Lett.* **2004**, *45* (22), 4289–4291.

(20) Patino, N.; Di Giorgio, C.; Dan-Covalciuc, C.; Peytou, V.; Terreux, R.; Cabrol-Bass, D.; Bailly, C.; Condom, R. Modelling, Synthesis and Biological Evaluation of an Ethidium-Arginine Conjugate

DOI: 10.1021/acscombsci.5b00089
ACS Comb. Sci. 2015, 17, 570–591

Linked to a Ribonuclease Mimic Directed Against TAR RNA of HIV-1. *Eur. J. Med. Chem.* **2002**, *37* (7), 573−584.
(21) Stuhr-Hansen, N.; Sølling, T. I.; Strømgaard, K. Synthetic and Mechanistic Insight into Nosylation of Glycine Residues. *Org. Biomol. Chem.* **2013**, *11* (14), 2288−2293.
(22) Miller, S. C.; Scanlan, T. S. Site-Selective *N*-Methylation of Peptides on Solid Support. *J. Am. Chem. Soc.* **1997**, *119* (9), 2301−2302.
(23) Yang, L.; Chiu, K. Solid Phase Synthesis of Fmoc *N*-Methyl Amino Acids: Application of the Fukuyama Amine Synthesis. *Tetrahedron Lett.* **1997**, *38* (42), 7307−7310.
(24) Bouillon, I.; Zajíček, J.; Pudelová, N.; Krchňák, V. Remarkably Efficient Synthesis of 2*H*-Indazole 1-Oxides and 2*H*-Indazoles via Tandem Carbon-Carbon Followed by Nitrogen-Nitrogen Bond Formation. *J. Org. Chem.* **2008**, *73* (22), 9027−9032.
(25) Schütznerová, E.; Krchňák, V. 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. *ACS Comb. Sci.* **2015**, *17* (2), 137−146.
(26) Smyslová, P.; Kisseljova, K.; Krchňák, V. Base-Mediated Intramolecular *C*- and *N*-Arylation of *N*,*N*-Disubstituted 2-Nitrobenzenesulfonamides: Advanced Intermediates for the Synthesis of Diverse Nitrogenous Heterocycles. *ACS Comb. Sci.* **2014**, *16* (9), 500−505.
(27) Hou, W.; Zhang, X.; Li, F.; Liu, C. F. Peptidyl *N*,*N*-Bis(2-mercaptoethyl)-amides as Thioester Precursors for Native Chemical Ligation. *Org. Lett.* **2011**, *13* (3), 386−389.
(28) Chhabra, S. R.; Khan, A. N.; Bycroft, B. W. Solid-Phase Synthesis of Polyamines Using a Dde-Linker: Philanthotoxin-4.3.3 via an On-Resin Mitsunobu Reaction. *Tetrahedron Lett.* **2000**, *41* (7), 1099−1102.
(29) Seo, J. s.; Kim, H. w.; Yoon, C. M.; Ha, D. C.; Gong, Y. D. Solid-Phase Synthesis of Hydroxypiperazine Derivatives Using Phenethylamine Linker by Oxidation-Cope Elimination. *Tetrahedron* **2005**, *61* (39), 9305−9311.
(30) Stanger, K. J.; Krchňák, V. Polymer-Supported *N*-Derivatized, *O*-Linked Hydroxylamine for Concurrent Solid-Phase Synthesis of Diverse *N*-Alkyl and *N*-H Hydroxamates. *J. Comb. Chem.* **2006**, *8* (3), 435−439.
(31) Le Pera, A.; Leggio, A.; Liguori, A. Highly Specific *N*-Monomethylation of Primary Aromatic Amines. *Tetrahedron* **2006**, *62* (25), 6100−6106.
(32) Tsuda, S.; Shigenaga, A.; Bando, K.; Otaka, A. N→S Acyl-Transfer-Mediated Synthesis of Peptide Thioesters Using Anilide Derivatives. *Org. Lett.* **2009**, *11* (4), 823−826.
(33) Christensen, C.; Clausen, R. P.; Begtrup, M.; Kristensen, J. L. Deprotection of 2-Nitrobenzenesulfonamides Using Fluorous and Solid Phase Reagents. *Tetrahedron Lett.* **2004**, *45* (43), 7991−7993.
(34) Otomaru, Y.; Tokunaga, N.; Shintani, R.; Hayashi, T. C2-Symmetric Bicyclo[3.3.1]nonadiene as a Chiral Ligand for Rhodium-Catalyzed Asymmetric Arylation of *N*-(4-Nitrobenzenesulfonyl)-arylimines. *Org. Lett.* **2005**, *7* (2), 307−310.
(35) Nihei, K. i.; Kato, M. J.; Yamane, T.; Palma, M. S.; Konno, K. 2-Nitro- and 2,4-Dinitrobenzenesulfonamides as Protecting Groups for Primary Amines. *Synlett* **2001**, *2001* (07), 1167−1169.
(36) Fang, W. J.; Yakovleva, T.; Aldrich, J. V. A Convenient Approach to Synthesizing Peptide *C*-Terminal *N*-Alkyl Amides. *Biopolymers* **2011**, *96* (6), 715−722.
(37) Cardullo, F.; Donati, D.; Merlo, G.; Paio, A.; Salaris, M.; Taddei, M. Deprotection of *o*-Nitrobenzensulfonyl (Nosyl) Derivatives of Amines Mediated by a Solid-Supported Thiol. *Synlett* **2005**, *2005* (19), 2996−2998.
(38) De Marco, R.; Di Gioia, M. L.; Leggio, A.; Liguori, A.; Viscomi, M. C. Deprotection of *N*-Nosyl-α-Amino Acids by Using Solid-Supported Mercaptoacetic Acid. *Eur. J. Org. Chem.* **2009**, *2009* (22), 3795−3800.
(39) De Rosa, M.; Stepani, N.; Cole, T.; Fried, J.; Huang-Pang, L.; Peacock, L.; Pro, M. Solid Phase Deprotection of 2-Nitrobenzenesulfonamides: Synthesis of Simple 2-(Alkylamino)-pyrroles. *Tetrahedron Lett.* **2005**, *46* (34), 5715−5717.
(40) Di Gioia, M. L.; Barattucci, A.; Bonaccorsi, P.; Leggio, A.; Minuti, L.; Romio, E.; Temperini, A.; Siciliano, C. Deprotection/Reprotection of the Amino group in α-Amino Acids and Peptides. A One-Pot Procedure in [Bmim][BF4] Ionic Liquid. *RSC Adv.* **2014**, *4* (6), 2678−2686.
(41) Miller, S. C.; Scanlan, T. S. *o*NBS-SPPS: A New Method for Solid-Phase Peptide Synthesis. *J. Am. Chem. Soc.* **1998**, *120* (11), 2690−2691.
(42) Biron, E.; Chatterjee, J.; Kessler, H. Optimized Selective *N*-Methylation of Peptides on Solid Support. *J. Pept. Sci.* **2006**, *12* (3), 213−219.
(43) Bolton, G. L.; Hodges, J. C. Solid-Phase Synthesis of Substituted Benzazepines via Intramolecular Heck Cyclization. *J. Comb. Chem.* **1999**, *1* (2), 130−133.
(44) Lemrová, B.; Soural, M. Solid-Phase Synthesis of 4,7,8-Trisubstituted 1,2,3,4-Tetrahydro-benzo[*e*][1,4]diazepin-5-ones. *ACS Comb. Sci.* **2012**, *14* (12), 645−650.
(45) Mohamed, N.; Bhatt, U.; Just, G. Efficient Synthesis of Substituted Oxopiperazines from Amino Acids. *Tetrahedron Lett.* **1998**, *39* (45), 8213−8216.
(46) Fülöpová, V.; Funk, P.; Popa, I.; McMaster, C.; Soural, M. Solid-Phase Synthesis of Trisubstituted Benzo[f]triazolodiazepin-6(5H)-ones and Their Sulfonyl Analogues under Mild Reaction Conditions. *Eur. J. Org. Chem.* **2015**, *2015* (16), 3551−3557.
(47) Pudelová, N.; Krchňák, V. Multiplicity of Diverse Heterocycles from Polymer-Supported α-Acylamino Ketones. *J. Comb. Chem.* **2009**, *11* (5), 851−859.
(48) Cankařová, N.; Krchňák, V. Solid-Phase Synthesis Enabling Chemical Diversity. In *Diversity-Oriented Synthesis*; Trabocchi, A., Ed.; John Wiley & Sons: Hoboken, NJ, 2013; pp 201−252.
(49) Kočí, J.; Pudelová, N.; Krchňák, V. Polymer-Supported α-Acylamino Ketones: Preparation and Application in Syntheses of 1,2,4-Trisubstituted-1*H*-imidazoles. *J. Comb. Chem.* **2009**, *11* (3), 397−402.
(50) Fülöpová, V.; Gucký, T.; Grepl, M.; Soural, M. Solid-Phase Synthesis of Trisubstituted Benzo[1,4]-Diazepin-5-one Derivatives. *ACS Comb. Sci.* **2012**, *14* (12), 651−656.
(51) Vézina-Dawod, S.; Derson, A.; Biron, E. *N*-Substituted Arylsulfonamide Building Blocks as Alternative Submonomers for Peptoid Synthesis. *Tetrahedron Lett.* **2015**, *56* (2), 382−385.
(52) Kay, C.; Murray, P. J.; Sandow, L.; Holmes, A. B. A Novel, Chemically Robust, Amine Releasing Linker. *Tetrahedron Lett.* **1997**, *38* (39), 6941−6944.
(53) Congreve, M. S.; Kay, C.; Scicinski, J. J.; Ley, S. V.; Williams, G.; Murray, P. J.; McKeown, S. C.; Watson, S. P. Versatile Solid-Phase Synthesis of Secondary Amines from Alcohols. Development of an *N*-Boc-(*o*-nitrobenzene)sulfonamide Linker. *Tetrahedron Lett.* **2003**, *44* (21), 4153−4156.
(54) Krchňák, V.; Slough, G. A. General Methodology for Solid-Phase Synthesis of *N*-Alkyl Hydroxamic Acids. *Tetrahedron Lett.* **2004**, *45* (24), 4649−4652.
(55) Krchňák, V. Biologically Interesting Compounds Containing Hydroxamic Acid Moiety. *Mini-Rev. Med. Chem.* **2006**, *6*, 27−36.
(56) Jensen, K. J.; Alsina, J.; Songster, M. F.; Vágner, J.; Albericio, F.; Barany, G. Backbone Amide Linker (BAL) Strategy for Solid-Phase Synthesis of *C*-Terminal-Modified and Cyclic Peptides1,2,3. *J. Am. Chem. Soc.* **1998**, *120* (22), 5441−5452.
(57) Olsen, C. A.; Witt, M.; Jaroszewski, J. W.; Franzyk, H. Diols as Building Blocks in Solid-Phase Synthesis of Polyamine Toxins by Fukuyama-Mitsunobu Alkylation. *Synlett* **2004**, *2004* (03), 473−476.
(58) 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* (25), 8820−8826.
(59) Berst, F.; Holmes, A. B.; Ladlow, M.; Murray, P. J. A Latent Aryl Hydrazine 'Safety-Catch' Linker Compatible with *N*-Alkylation. *Tetrahedron Lett.* **2000**, *41* (34), 6649−6653.
(60) Koide, K.; Finkelstein, J. M.; Ball, Z.; Verdine, G. L. A Synthetic Library of Cell-Permeable Molecules. *J. Am. Chem. Soc.* **2001**, *123* (3), 398−408.
(61) Cankařová, N.; Krchňák, V. Polymer-Supported Stereoselective Synthesis of Benzimidazolinopiperazinones. *J. Org. Chem.* **2012**, *77* (13), 5687−5695.

DOI: 10.1021/acscombsci.5b00089
ACS Comb. Sci. 2015, 17, 570−591

(62) Schütznerová, E.; Oliver, A. G.; Zajíček, J.; Krchňák, V. Polymer-Supported Stereoselective Synthesis of (1*S*,5*S*)-6-Oxa-3,8-diazabicyclo-[3.2.1]octanes. *Eur. J. Org. Chem.* **2013**, *2013* (15), 3158−3165.
(63) La Venia, A.; Lemrová, B.; Krchňák, V. Regioselective Incorporation of Backbone Constraints Compatible with Traditional Solid-Phase Peptide Synthesis. *ACS Comb. Sci.* **2013**, *15* (1), 59−72.
(64) La Venia, A.; Dolenský, B.; Krchňák, V. Polymer-Supported Stereoselective Synthesis of Tetrahydro-2*H*-oxazolo[3,2-*a*]pyrazin-5(3*H*)-ones from *N*-(2-Oxo-ethyl)-Derivatized Dipeptides via East-bound Iminiums. *ACS Comb. Sci.* **2013**, *15* (3), 162−167.
(65) Arya, P.; Wei, C. Q.; Barnes, M. L.; Daroszewska, M. A Solid Phase Library Synthesis of Hydroxyindoline-Derived Tricyclic Derivatives by Mitsunobu Approach. *J. Comb. Chem.* **2004**, *6* (1), 65−72.
(66) Bianchi, I.; La Porta, E.; Barlocco, D.; Raveglia, L. F. Solid-Phase Convergent Synthesis of a Benzimidazolone Library via the Combination of Two Smaller Arrays of Carboxylic Acids and Secondary Amines. *J. Comb. Chem.* **2004**, *6* (5), 835−845.
(67) Di Gioia, M. L.; Leggio, A.; Liguori, A.; Perri, F. Solid-Phase Synthesis of *N*-Nosyl- and *N*-Fmoc-*N*-Methyl-α-amino Acids. *J. Org. Chem.* **2007**, *72* (10), 3723−3728.
(68) Ventosa-Andrés, P.; Hradilová, L.; Krchňák, V. Privileged Structures as Peptide Backbone Constraints: Polymer-Supported Stereoselective Synthesis of Benzimidazolinopiperazinone Peptides. *ACS Comb. Sci.* **2014**, *16* (7), 359−366.
(69) La-Venia, A.; Ventosa-Andrés, P.; Hradilová, L.; Krchňák, V. From Amino Acids to Nature-Inspired Molecular Scaffolds: Incorporation of Medium-Sized Bridged Heterocycles into a Peptide Backbone. *J. Org. Chem.* **2014**, *79* (21), 10378−10389.
(70) Vaňková, B.; Brulíková, L.; Wu, B.; Krchňák, V. Synthesis of Piperazinones, Piperazines, Tetrahydropyrazines, and Dihydropyrazinones from Polymer-Supported Acyclic Intermediates via *N*-Alkyl- and *N*-Acyliminiums. *Eur. J. Org. Chem.* **2012**, *2012* (26), 5075−5084.
(71) Peng, G.; Sohn, A.; Gallop, M. A. Stereoselective Solid-Phase Synthesis of a Triaza Tricyclic Ring System: A New Chemotype for Lead Discovery. *J. Org. Chem.* **1999**, *64* (22), 8342−8349.
(72) Olsen, C. A.; Christensen, C.; Nielsen, B.; Farah, M. M.; Witt, M.; Clausen, R. P.; Kristensen, J. L.; Franzyk, H.; Jaroszewski, J. W. Aminolysis of Resin-Bound *N*-Nosylaziridine-2-carboxylic Acids. *Org. Lett.* **2006**, *8* (15), 3371−3374.
(73) Stanger, K. J.; Sliva, D.; Jiang, J.; Krchňák, V. Synthesis and Screening of *N*-Alkyl Hydroxamates for Inhibition of Cancer Cell Proliferation. *Comb. Chem. High Throughput Screening* **2006**, *9* (9), 651−661.
(74) Cankařová, N.; La Venia, A.; Krchňák, V. Polymer-Supported Stereoselective Synthesis of Tetrahydrobenzopyrazino-thiadiazinone Dioxides via *N*-Sulfonyl Iminiums. *ACS Comb. Sci.* **2014**, *16* (6), 293−302.
(75) Fülöpová, V.; Krchňák, V. Solid-Phase Synthesis of Trisubstituted 2,5-Dihydrobenzo[*f*][1,2,5]thiadiazepine 1,1-Dioxide Derivatives. *ACS Comb. Sci.* **2014**, *16* (8), 412−420.
(76) Fülöpová, V.; Krchňáková, A.; Schütznerová, E.; Zajíček, J.; Krchňák, V. Ring Contraction of 2,5-Dihydrobenzo[*f*][1,2,5]-thiadiazepine 1,1-Dioxides: Access to 4*H*-Benzo[*b*][1,4]thiazine 1,1-Dioxides. *J. Org. Chem.* **2015**, *80* (3), 1795−1801.
(77) Kisseljova, K.; Smyslová, P.; Krchňák, V. Benzhydrylamines via Base-Mediated Intramolecular sp^3 *C*-Arylation of *N*-Benzyl-2-nitrobenzenesulfonamides-Advanced Intermediates for the Synthesis of Nitrogenous Heterocycles. *ACS Comb. Sci.* **2014**, *16* (10), 573−577.
(78) Pudelová, N.; Krchňák, V. Efficient Traceless Solid-Phase Synthesis of 3,4-Dihydropyrazino[1,2-*b*]indazoles and Their 6-Oxides. *J. Comb. Chem.* **2009**, *11* (3), 370−374.
(79) Kočí, J.; Krchňák, 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* (1), 168−175.
(80) Kočí, J.; Oliver, A. G.; Krchňák, V. Unprecedented Rearrangement of 2-(2-Aminoethyl)-1-aryl-3,4-dihydropyrazino[1,2-*b*]indazole-2-ium 6-oxides to 2,3-Dihydro-1*H*-imidazo[1,2-*b*]indazoles. *J. Org. Chem.* **2010**, *75* (2), 502−505.
(81) Morimoto, Y.; Kurihara, H.; Yokoe, C.; Kinoshita, T. New Aspect of Methanesulfonyl Chloride: Unusual Deoxygenations of Pyridine *N*-Oxides with Methanesulfonyl Chloride and Triethylamine. *Chem. Lett.* **1998**, *27* (8), 829−830.
(82) Křupková, S.; Slough, G. A.; Krchňák, 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* (13), 4562−4566.
(83) Fukuyama, T.; Cheung, M.; Jow, C. K.; Hidai, Y.; Kan, T. 2,4-Dinitrobenzenesulfonamides: A Simple and Practical Method for the Preparation of a Variety of Secondary Amines and Diamines. *Tetrahedron Lett.* **1997**, *38* (33), 5831−5834.
(84) 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* (6), 1647−1656.
(85) 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**, *33*, 5012−5014.
(86) Bisegger, P.; Manov, N.; Bienz, S. Solid-Phase Synthesis of Cyclic Polyamines. *Tetrahedron* **2008**, *64* (32), 7531−7536.
(87) Richter, H.; Jung, G. Substituted Sulfonamides via a Three Component Reaction on Solid Support. *Tetrahedron Lett.* **1998**, *39* (18), 2729−2730.
(88) Campian, E.; Lou, B.; Saneii, H. Solid-Phase Synthesis of α-Sulfonylamino Amide Derivatives Based on Ugi-Type Condensation Reaction Using Sulfonamides as Amine Input. *Tetrahedron Lett.* **2002**, *43* (47), 8467−8470.
(89) Maclean, D.; Hale, R.; Chen, M. The Reversed Kenner Linker: A New Safety-Catch Linker for the Preparation of *N*-Alkyl Sulfonamides. *Org. Lett.* **2001**, *3* (19), 2977−2980.
(90) Kenner, G. W.; McDermott, J. R.; Sheppard, R. C. The Safety Catch Principle in Solid Phase Peptide Synthesis. *J. Chem. Soc. D* **1971**, *12*, 636−637.
(91) Renault, J.; Fabis, F.; Dauphin, F.; Lebranchu, M.; Roch, M. L.; Butt, S.; Uriac, P.; Rault, S. Solid Phase Synthesis of Sulphonamides: Novel Ligands of 5-HT_6 Receptors. *J. Pharm. Pharmacol.* **2001**, *53* (7), 969−972.
(92) Nicolaou, K. C.; Pfefferkorn, J. A.; Mitchell, H. J.; Roecker, A. J.; Barluenga, S.; Cao, G. Q.; Affleck, R. L.; Lillig, J. E. Natural Product-Like Combinatorial Libraries Based on Privileged Structures. 2. Construction of a 10 000-Membered Benzopyran Library by Directed Split-and-Pool Chemistry Using NanoKans and Optical Encoding. *J. Am. Chem. Soc.* **2000**, *122* (41), 9954−9967.
(93) Nicolaou, K. C.; Pfefferkorn, J. A.; Barluenga, S.; Mitchell, H. J.; Roecker, A. J.; Cao, G. Q. Natural Product-Like Combinatorial Libraries Based on Privileged Structures. 3. The "Libraries from Libraries" Principle for Diversity Enhancement of Benzopyran Libraries. *J. Am. Chem. Soc.* **2000**, *122* (41), 9968−9976.
(94) Makino, S.; Nakanishi, E.; Tsuji, T. Efficient Synthesis of 2,4-Disubstituted 1,2,4-Benzothiadiazin-3-one 1,1-Dioxides on Solid Support. *J. Comb. Chem.* **2003**, *5* (1), 73−78.
(95) McMaster, C.; Fülöpová, V.; Popa, I.; Grepl, M.; Soural, M. Solid-Phase Synthesis of Anagrelide Sulfonyl Analogues. *ACS Comb. Sci.* **2014**, *16* (5), 221−224.
(96) Hlaváč, J.; Soural, M.; Krchňák, V. Practical Aspects of Combinatorial Solid-Phase Synthesis. In *Solid-Phase Organic Synthesis*; Toy, P. H., Lam, Y., Eds.; John Wiley & Sons: Hoboken, NJ, 2011; pp 95−130.

DOI: 10.1021/acscombsci.5b00089
ACS Comb. Sci. 2015, 17, 570−591