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Aminolysis of Resin-Bound *N*-Nosylaziridine-2-carboxylic Acids

Christian A. Olsen,*,† Caspar Christensen,† Birgitte Nielsen,† Farah M. Mohamed,† Matthias Witt,‡ Rasmus P. Clausen,† Jesper L. Kristensen,† Henrik Franzyk,† and Jerzy W. Jaroszewski†

Department of Medicinal Chemistry, The Danish University of Pharmaceutical Sciences, DK-2100 Copenhagen, Denmark, and Bruker Daltonik GmbH, Fahrenheitstrasse 4, D-28359 Bremen, Germany

cao@dfuni.dk

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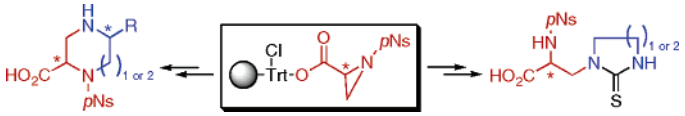
ABSTRACT



Solid-phase synthesis is a rapidly developing area of organic chemistry, of particular importance for medicinal chemistry and chemical biology. Aziridines have previously only rarely been applied in solid-phase synthesis. In the present work, aminolysis of resin-bound, spring-loaded *N*-nitrobenzenesulfonyl-activated aziridine-2-carboxylic acids has been optimized and employed in the synthesis of a number of open-chain and heterocyclic scaffolds, including enantiopure products.

Nucleophilic ring opening of N-activated aziridines is a highly efficient transformation in organic synthesis.[1] Aziridines were recently applied in solid-phase synthesis (SPS) of thioglycopeptide derivatives by Gin, van der Donk, and co-workers.[2,3] Their approach consisted of ring opening of resin-bound peptide substrates containing aziridine-2-carboxylic acid (Azy-OH) residues with various sulfur nucleophiles,[2,3] and ring-opening reactions with selenium nucleophiles were also demonstrated by this group.[4] However, the number of reactions employing resin-bound aziridines is still very limited.[5−7]

SPS technology is extremely useful for parallel synthesis of compound collections, and especially, handling large numbers of compounds in split-pool combinatorial libraries is more convenient using SPS methods. We argue that the development of efficient synthetic tools for SPS is important to obtain diverse compound collections for biological screening in the future.

In the present paper, we describe the first examples of aminolysis of aziridines on solid phase. Aziridines were activated with *o*- or *p*-nitrobenzenesulfonyl (nosyl = Ns) groups, and the ring-opening reactions were optimized for expeditious preparation of mono-N-protected α,β-diamino acids and rigid heterocyclic scaffolds based on the diamino acid motifs.

The use of a nosyl group for activation of aziridines seemed attractive due to its versatility, both as an activating group (in Fukuyama alkylations) and as a protecting group (for secondary amines) readily removable with sulfur nucleophiles.[8,9] Initially, a polystyrene Wang resin preloaded with glycine was derivatized with *o*Ns-Azy-OH or *p*Ns-Azy-

* To whom correspondence should be addressed. Phone: +45-35306499. Fax: +45-35306041.
† The Danish University of Pharmaceutical Sciences.
‡ Bruker Daltonik GmbH.

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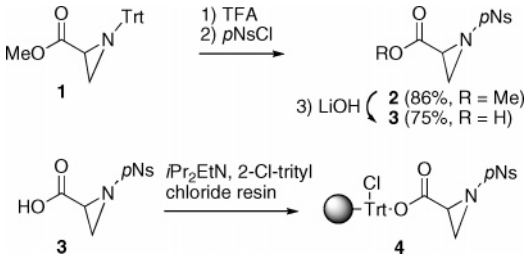
OH, and the resulting resins were treated with primary amine nucleophiles under a variety of conditions. The use of *p*Ns activation resulted in a higher degree of conversion compared to the *o*Ns group in all solvents tested; however, the observed gain in reactivity occurred at the expense of diminished regioselectivity for the attack at C-3 (see the Supporting Information, Table S1). Generally, sulfonamide-activated aziridines are preferentially attacked at the least-hindered carbon atom,[10] but an altered selectivity has previously been reported in the presence of adjacent electron-withdrawing substituents.[11a] Hence, the presence of the carbonyl group in the *p*Ns-Azy moiety accounts for a diminished selectivity for the nucleophilic substitution at C-3 due to enhanced electrophilicity of C-2. To circumvent this problem, *p*Ns-Azy-OH (**3**) (prepared in three steps from **1**) was loaded onto a polystyrene 2-chlorotrityl resin to give **4** (Scheme 1, see the Supporting Information for details).

Scheme 1. Preparation and Loading of *p*Ns-Azy-OH[a]



[a] TFA = trifluoroacetic acid.

The ensuing increase of steric congestion in the vicinity of C-2 was expected to improve regioselectivity, as in the work of Baldwin and co-workers, who observed preferential attack of organocuprates on C-3 in *tert*-butyl *N*-toluenesulfonylaziridine-2-carboxylate in solution.[11]

Exploratory aminolysis experiments using resin **4** and *n*-propylamine in THF or DMF furnished compound **7a** in good purity as judged by ^{1}H NMR and RP-HPLC.[12] The steric bulk of the 2-chlorotrityl linker provided the anticipated effect on the regioselectivity, as evidenced by the COSY connectivities observed for compound **7a** (see Figure 1). Furthermore, the ^{1}H NMR spectrum of crude **7a**, showing that the expected regioisomer is highly predominant before

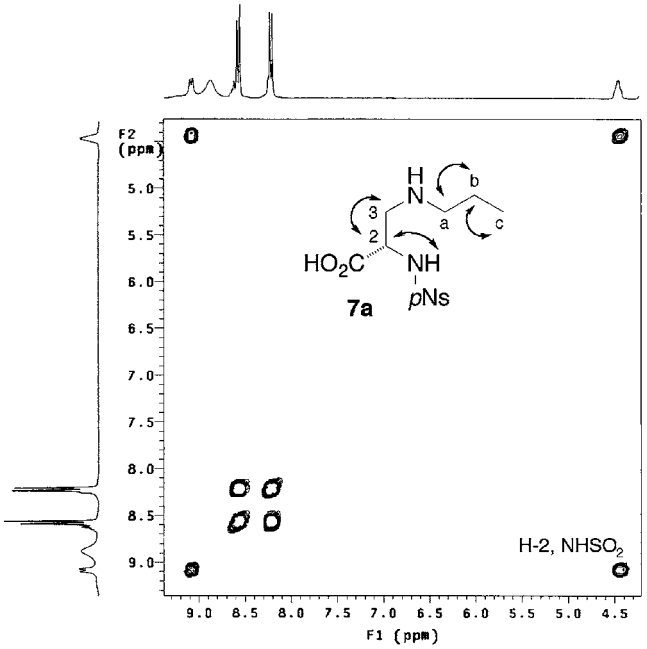
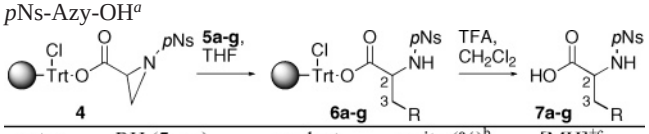
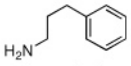
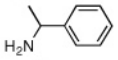
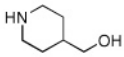
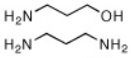
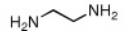


Figure 1. Section of the COSY spectrum of **7a** obtained in dimethyl sulfoxide-d_6, showing a well-resolved signal of the $NHSO_2$ hydrogen. The structure inset shows the observed COSY connectivities.

purification, is included in the Supporting Information. Very high conversions as well as good purities were obtained with a variety of amines, amino alcohols, and diamines using THF as solvent (Table 1). The RP-HPLC purities were lower when using diamine nucleophiles, most likely due to cross-linking/

Table 1. Aminolysis of 2-Chlorotrityl Resin-Bound *p*Ns-Azy-OH[a]



entry	RH (**5a–g**)	product	purity (%)[b]	[MH]$^{+}$[c]
1		**7a**	88	332.1
2		**7b**	88	408.2
3		**7c**	83	394.1
4		**7d**	82	388.2
5		**7e**	81	348.1
6		**7f**	53	347.1
7		**7g**	56	333.1

[a] Portions of resin **4** (100 mg) were agitated with the appropriate nucleophile (**5a**−**g**, 4 equiv) in THF for 16 h at 21 °C, to give resins **6a**−**g**; the products were cleaved with TFA−CH_2Cl_2−Et_3SiH 47.5:47.5:5 (50 min) and dried in vacuo. [b] Determined by RP-HPLC (254 nm). [c] ESI-MS data obtained with the collected fractions from RP-HPLC were all in agreement with calculated values; furthermore, the purities and identities of all products from these fractions were confirmed by analytical HPLC and HRMS, respectively.

(9) Previously, nitrobenzenesulfonyl-activated aziridines have been successfully ring opened with amine nucleophiles in solution. See: (a) Maligres, P. E.; See, M. M.; Askin, D.; Reider, P. J. *Tetrahedron Lett.* **1997**, *38*, 5253−5256. (b) Turner, J. J.; Sikkema, F. D.; Filippov, D. V.; van der Marel, G. A.; van Boom, J. H. *Synlett* **2001**, 1727−1730. (c) Kim, B. M.; So, S. M.; Choi, H. J. *Org. Lett.* **2002**, *4*, 949−952.

(10) For reviews on aziridine chemistry, see: (a) Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599−619. (b) Hu, E. X. *Tetrahedron* **2004**, *60*, 2701−2742.

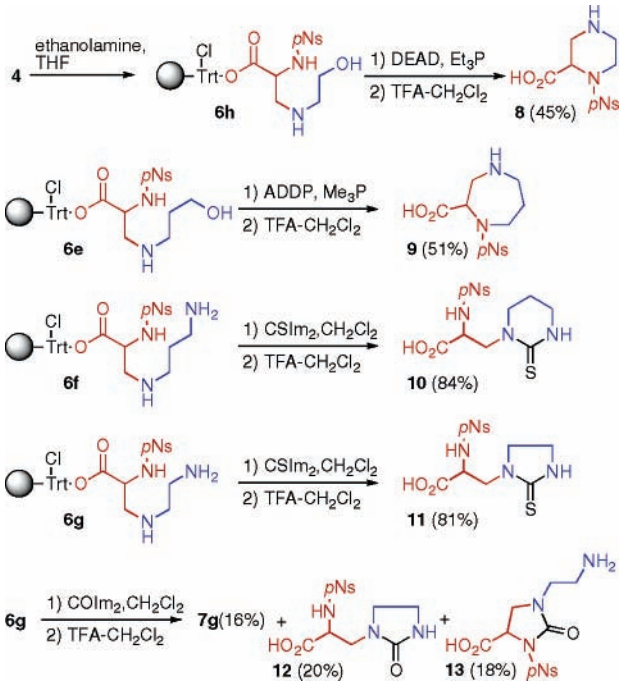
(11) (a) Baldwin, J. E.; Spivey, A. C.; Schofield, C. J.; Sweeney, J. B. *Tetrahedron* **1993**, *49*, 6309−6330. (b) A similar regioselectivity was also described with unprotected acids: Churh, N. J.; Young, D. W. *Tetrahedron Lett.* **1995**, *36*, 151−154.

(12) The preliminary aminolysis experiments with nPrNH$_2$ were performed with 4, 8, or 20 equiv of the amine in THF or DMF; both the ^{1}H NMR data and the RP-HPLC traces suggested equally high conversions/yields in all six cases.

site−site interactions as previously described for S_N2 reactions on solid phase by us and others.[13]

The scope of this high-yielding, regioselective transformation was explored by the preparation of a number of rigid scaffolds. Thus, resins **6h** and **6e** were successfully cyclized by intramolecular Fukuyama−Mitsunobu reactions[14] to give mono-N-protected diamino acids **8** and **9**, respectively (Scheme 2). Initially, 1,1′-(azodicarbonyl)dipiperidide (ADDP)

Scheme 2. Fukuyama−Mitsunobu Cyclization of Resin-Bound Intermediates Obtained by Ring Opening of *p*Ns-Azy Resins[a]



[a] Crude RP-HPLC purities are given in parentheses; the purities and identities of all products were confirmed by analytical HPLC and HRMS, respectively.

and Me_3P were applied as the coupling reagents.[15] This reagent pair performed satisfactorily for the synthesis of 1,4-diazepanecarboxylic acid **9** but afforded primarily a noncyclized product upon attempted ring closure of resin **6h**, followed by cleavage from the linker. However, diethyl azodicarboxylate (DEAD) in combination with Et_3P furnished the target piperazinecarboxylic acid **8** in acceptable yield.[16]

Thus, expedient two-step syntheses of rigid scaffolds, containing two secondary amino functionalities for further appendage diversification, were possible owing to the efficient aminolysis of resin **4** with unprotected amino alcohols. Furthermore, resins **6f** and **6g** (Table 1), obtained using unprotected diamines as nucleophiles, were cyclized to N-protected amino acids **10**−**12** with 1,1′-thiocarbonyldiimidazole ($CSIm_2$) and 1,1′-carbonyldiimidazole ($COIm_2$). Similar derivatizations of tri- and polyamines have previously been explored by Houghten and co-workers.[17] Fortunately, the above-mentioned site−site interaction on the resin did not lead to substantial amounts of by-products in these cases. On the other hand, the byproduct **13** that arises from condensation with the nosylamide functionality was observed when using the $COIm_2$ reagent (Scheme 2).

The above examples of efficient SPS aziridine chemistry employed racemic (*R*,*S*)-*p*Ns-Azy-OH (**3**). As the absolute stereochemistry is important in relation to the biological activity of small-molecule probes, the enantiopure (*S*)-*p*Ns-Azy-OH (***S*-3**) building block was prepared and loaded onto the 2-chlorotrityl resin to give **14**. To determine the optical purity of ***S*-3**, its enantiomer (*R*)-*p*Ns-Azy-OH (***R*-3**) was also prepared, and the enantiomeric excess (ee) was determined to be >98% by chiral HPLC analysis.[18,19] The resin **14** enabled synthesis of rigid diamino acid enantiomers **15** and **16** by reaction with (*S*)-phenylalaninol or (*S*)-alaninol, respectively (Scheme 3).[20] ^{1}H NMR spectra of the crude products of these reactions showed no sign of the presence of the corresponding cis-disubstituted piperazines, i.e., no evidence of racemization at C-2 (see the Supporting Information). Interestingly, our attempts to prepare the corresponding diastereomers using (*R*)-phenylalaninol failed, and a diminished yield was observed in the case of (*R*)-alaninol (Scheme 3).

Thus, the Fukuyama−Mitsunobu cyclization appears to proceed inefficiently for the stereoisomer combination *S*,*R*.

(13) (a) Basso, A.; Bradley, M. *Tetrahedron Lett.* **2003**, *44*, 2699−2702. (b) Olsen, C. A.; Witt, M.; Jaroszewski, J. W.; Franzyk, H. *Org. Lett.* **2004**, *6*, 1935−1938.

(14) For previous examples of intramolecular Fukuyama−Mitsunobu reactions on solid phase, see: (a) Kung, P. P.; Swayze, E. *Tetrahedron Lett.* **1999**, *40*, 6551−5654. (b) Arya, P.; Wei, C.-Q.; Barnes, M. L.; Daroszewska, M. *J. Comb. Chem.* **2004**, *6*, 65−72.

(15) Previously employed in polyamine synthesis on solid phase: (a) Olsen, C. A.; Witt, M.; Jaroszewski, J. W.; Franzyk, H. *Synlett* **2004**, 473−476. (b) Olsen, C. A.; Witt, M.; Hansen, S. H.; Jaroszewski, J. W.; Franzyk, H. *Tetrahedron* **2005**, *61*, 6046−6055.

(16) Selected reagent pairs (see also ref 15b) gave the following crude RP-HPLC purities: DEAD-Ph_3P, 36%; DEAD-Et_3P, 45%; ADDP-Et_3P, 40%.

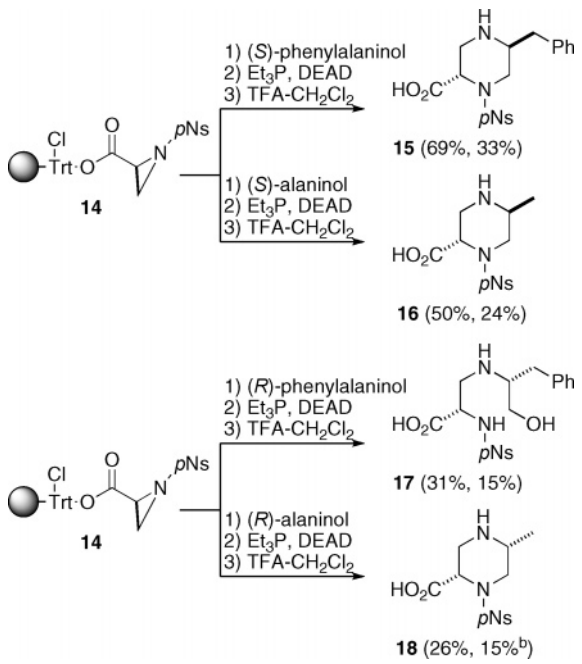
(17) For representative examples, see: (a) Nefzi, A.; Ostresh, J. M.; Giulianotti, M. A.; Houghten, R. A. *J. Comb. Chem.* **1999**, *1*, 195−198. (b) Nefzi, A.; Giulianotti, M. A.; Ong, N. A.; Houghten, R. A. *Org. Lett.* **2000**, *2*, 3349−3350. (c) Nefzi, A.; Giulianotti, M. A.; Houghten, R. A. *J. Comb. Chem.* **2001**, *3*, 68−70. (d) Acharya, A. N.; Ostresh, J. M.; Houghten, R. A. *J. Comb. Chem.* **2001**, *3*, 612−623. (e) Nefzi, A.; Giulianotti, M. A.; Truong, L.; Rattan, S.; Ostresh, J. M.; Houghten, R. A. *J. Comb. Chem.* **2002**, *4*, 175−178. (f) Nefzi, A.; Ostresh, J. M.; Yu, J.; Houghten, R. A. *J. Org. Chem.* **2004**, *69*, 3603−3609.

(18) The HPLC system was operated isocratically with a 9:1 mixture of 15 mM NH_4OAc buffer (pH 4.1) and EtOH at a flow rate of 0.5 mL/min. A serial connection of two 50 mm and two 150 mm Astec Chirobiotic T (4.6 ID) columns was used to obtain acceptable retention times: t_R (***S*-3**) = 15.4 min and t_R (***R*-3**) = 14.4 min.

(19) Optical rotations were determined as follows: ***S*-3**, $[\alpha]^{25}_D$ −40.4° (*c* 1.6, MeOH); ***R*-3**, $[\alpha]^{25}_D$ +45.2° (*c* 1.4, MeOH).

(20) Representative procedure leading to compound **15**: (*S*)-*p*Ns-Azy-loaded 2-chlorotrityl resin (**14**, 240 mg, 100 μmol) was swelled in distilled CH_2Cl_2 under N_2 for 5 min, drained, and agitated with (*S*)-phenylalaninol (60 mg, 400 μmol, 4 equiv) in THF (2 mL) for 16 h at 21 °C under N_2. After washing with DMF (3×), MeOH (3×), and CH_2Cl_2 (3×), the resin was dried in vacuo. Distilled CH_2Cl_2 (1 mL) was added, followed by Et_3P (1 mL of a 1 M solution in THF, 1 mmol, 10 equiv) and DEAD (80 μL, 500 μmol, 5 equiv), and the mixture was shaken for 2 h under N_2. This procedure was repeated with shaking for 12 h. The resin was drained and washed with DMF (3×), MeOH (3×), and CH_2Cl_2 (3×), and the product was cleaved off with TFA−CH_2Cl_2 1:1 (1.5 mL, 30 min). The cleavage mixture and washings (CH_2Cl_2 and MeOH) were pooled, and the solvents were removed in vacuo. The crude material was dissolved in MeCN (1 mL) and purified by preparative RP-HPLC (17 mg, 33%).

Scheme 3. Preparation of Enantiopure Piperazinecarboxylic Acid Derivatives[a]



[a] Crude RP-HPLC purities and isolated yields based on the loading of **14** are shown in parentheses. [b] A 1:2 mixture of **18** and its noncyclized precursor as estimated from LC-MS.

This is presumably due to an unfavorable, axial orientation of the methyl or benzyl substituent in the transition state for the latter combination (Figure 2). Applying more forcing

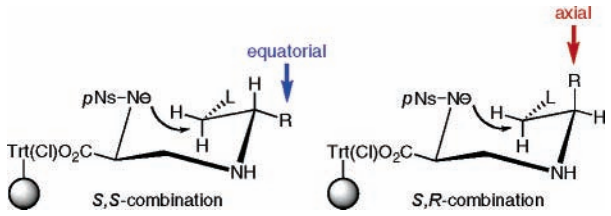


Figure 2. Proposed substrate conformations for the intramolecular Fukuyama−Mitsunobu cyclizations of the *S*,*S* and *S*,*R* combinations of *p*Ns-Azy-OH and phenylalaninol (R = CH_2Ph) or alaninol (R = Me); L = $OPEt_3^+$ (leaving group).

reaction conditions resulted in complex reaction mixtures, which were not further analyzed. Nevertheless, the availability of enantiopure ***S*-3** and ***R*-3** allows further diversification of their ring-opening products with respect to absolute stereochemistry; libraries of diamino acids employing both of these building blocks are in preparation and will be reported separately.

We conclude that on-resin aziridine aminolysis represents a useful addition to the toolbox for SPS of compounds with amino functionalities.[21] In addition, it allows the synthesis of enantiopure products from *p*Ns-Azy-OH enantiomers and optically active nucleophiles. Utilization of the wide variety of commercially available, enantiopure amino alcohols derived from α- and *β*-amino acids enables an easy access to a large number of constrained diamino acid scaffolds with two stereocenters and several handles potentially useful for subsequent appendage diversification,[22] which supplements skeletal and stereochemical diversity of scaffolds.[23] The chemistry described in the present work allows preparation of scaffolds of a relatively low complexity, but having privileged structures widely applied in medicinal chemistry. Accordingly, solid-phase aziridine chemistry has a potential for future applications in the forward synthetic planning of DOS libraries,[23] possibly also in combination with direct, on-resin aziridination.[24]

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Supporting Information Available: Materials, experimental procedures, results of ring-opening experiments (Table S1), compound characterization data, copies of HPLC traces of crude **7a**−**g** and **8**−**11**, copies of ^{1}H NMR and ^{13}C NMR spectra of compounds ***S*-2**, ***S*-3**, ***S*-7a**, and **15**−**17**, as well as ^{1}H NMR of crude **7a** and COSY of **7a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) For a comprehensive review of previously available methods for formation of the amino functionality of solid phase, see: Olsen, C. A.; Franzyk, H.; Jaroszewski, J. W. *Synthesis* **2005**, 2631−2653.

(22) For examples of DOS based on privileged structures/scaffolds, see: (a) Nicolaou, K. C.; Pfefferkorn, J. A.; Roecker, A. J.; Cao, G.-Q.; Barluenga, S.; Mitchell, H. J. *J. Am. Chem. Soc.* **2000**, *122*, 9939−9953. (b) Nicolaou, K. C.; Pfefferkorn, J. A.; Mitchell, H. J.; Roecker, A. J.; Barluenga, S.; Cao, G.-Q.; Affleck, R. L.; Lillig, J. E. *J. Am. Chem. Soc.* **2000**, *122*, 9954−9967. (c) Nicolaou, K. C.; Pfefferkorn, J. A.; Barluenga, S.; Mitchell, H. J.; Roecker, A. J.; Cao, G.-Q. *J. Am. Chem. Soc.* **2000**, *122*, 9968−9976. (d) Pelish, H. E.; Westwood, N. J.; Feng, Y.; Kirchhausen, T.; Shair, M. D. *J. Am. Chem. Soc.* **2001**, *123*, 6740−6741. (e) Ding, S.; Gray, N. S.; Wu, X.; Ding, Q.; Schultz, P. G. *J. Am. Chem. Soc.* **2002**, *124*, 1594−1595.

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