JOC Note

Microwave-Assisted Ring-Opening of Activated Aziridines with Resin-Bound Amines

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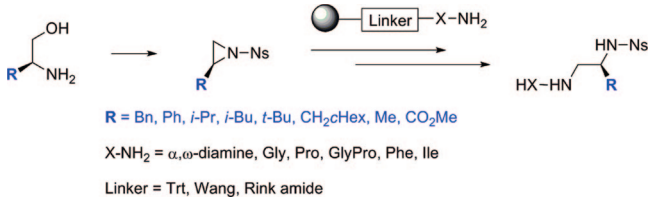
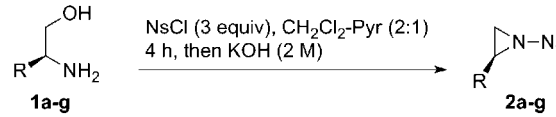


This paper describes the first study of nucleophilic ring-opening of nosylamide-activated aziridines under microwave irradiation conditions in solid-phase synthesis (SPS). The effects of solvent, temperature, reaction time, and reagent ratio in SPS of partially protected triamines from aziridines and resin-bound diamines were investigated. The methodology was also optimized for the synthesis of novel amino acid derivatives.

During the past decade, ring-opening of aziridines with a wide range of nucleophiles has become an important versatile synthetic tool for organic chemists in the preparation of interesting compounds and intermediates for biological applications.[1] Regardless of recent developments in aziridine chemistry, only very few papers concerning the utilization of aziridine building blocks in solid-phase synthesis (SPS) have appeared.[2,3] Recently, Galonic and co-workers realized the ring-opening of resin-bound peptidic substrates containing aziridine residues with sulfur and selenium nucleophiles.[4] Moreover, Olsen and co-workers have explored aminolysis of resin-bound *N*-(*p*-nitrobenzenesulfonyl)aziridine-2-carboxylic acid with different amines and amino alcohols.[5] However, resin-bound amine nucleophiles have apparently never been used in ring-opening of aziridines.

SCHEME 1. Preparation of *p*-Nitrobenzenesulfonyl-Activated Aziridine Building Blocks 2a−g



a: R = Bn (83%) **c**: R = Ph (82%) **e**: R = CH_2cHex (78%)
b: R = *i*-Pr (83%) **d**: R = *i*-Bu (87%) **f**: R = *t*-Bu (82%)
g: R = Me (quant.)

Herein, we report on nucleophilic ring-opening of *p*-nitrobenzenesulfonyl (nosyl = Ns)-activated aziridines employing a resin-bound diamine under microwave irradiation. This methodology was extended to include synthesis of novel amino acid derivatives. The simplest synthetic route to activated aziridine building blocks generally comprises *N*-protection and *O*-activation of 1,2-amino alcohols, followed by in situ aziridine formation.[6],,,, We decided to use the one-pot procedure recently described by Farràs and co-workers (Scheme 1).[7]

Thus, chiral *N*-nosylaziridines **2a**−**g** were obtained in very good yields by reaction of commercially available chiral 1,2-amino alcohols **1a**−**g** with an excess of *p*-nitrobenzenesulfonyl chloride (NsCl) in CH_2Cl_2−pyridine (2:1) followed by an alkaline workup. In the synthesis of the novel cyclohexylmethyl (CH_2cHex)-substituted building block **2e**, the starting hydrochloride of the corresponding amino alcohol required addition of 1 equiv of triethylamine prior to the addition of NsCl.[8]

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(8) The sign of the specific optical rotation ($[\alpha]_D$) of **2e** was opposite to that of other aziridine building blocks with similar stereochemistry, but crystallization and subsequent X-ray structure determination confirmed unequivocally its stereochemistry. For details of crystallographic data of compounds **2c** and **2e**, see the Supporting Information.

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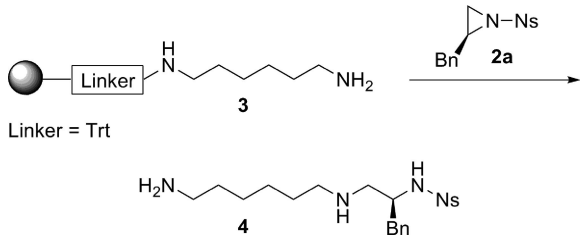
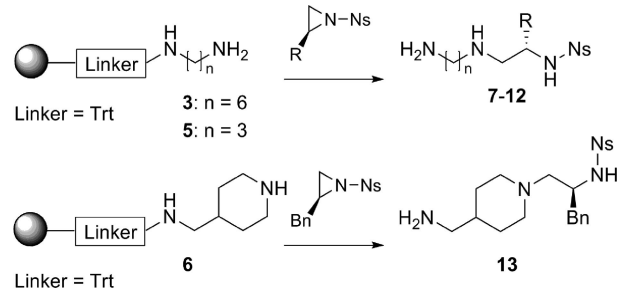
TABLE 1. Study of Microwave-Assisted Ring-Opening of Nosyl-Activated Aziridine 2a with Resin 3[a]



entry	equiv of **2a**	*T* (°C)	time (min)	% purity[b]	% yield[c]
1	1	80	30	85	>80
2	2	80	30	88	>90
3	3	80	30	76	>85
4	2	60	15	83	>85
5	2	80	15	82	>90
6	2	110	15	73	>90
7	1	60	30	90	>70
8	1	60	5	96	>70

[a] Portions of resin **3** (25 mg with a loading of 1.2 mmol·g^{-1}) were reacted in DCE (1 mL). Resins were cleaved with TFA−CH_2Cl_2 (20:80), and the mixtures were coevaporated with toluene and dried in vacuo to give crude **4** as a bis(TFA) salt. [b] Determined by HPLC (254 nm). [c] Yields were estimated from the amount of crude product and the initial resin loading.

TABLE 2. Extension of MW-Assisted Ring-Opening to More Hindered Aziridines and a Resin-Bound Secondary Amine[a]



entry	resin	aziridine	% purity	% yield	product
1	**3**	**2d**	79	>50	**7**
2	**3**	**2e**	79	>55	**8**
3	**3**	**2f**	63	>25	**9**
4	**5**	**2a**	91	>75	**10**
5	**5**	**2b**	93	>85	**11**
6	**5**	**2c**	94	>85	**12**
7	**6**	**2a**	97	>95	**13**

[a] Portions of resin (120 mg of **3** with a loading of 1.5 mmol·g^{-1}, 30 mg of **5** with a loading of 1.8 mmol·g^{-1}, or 50 mg of **6** with a loading of 0.83 mmol·g^{-1}) and 2 equiv of the respective aziridine building block were stirred under MW conditions in DCE (1 mL) for 5 min at 60 °C. Cleavage with TFA−CH_2Cl_2 (20:80), coevaporation with toluene, and drying in vacuo gave the corresponding crude products.

In order to find suitable conditions for efficient microwave-assisted ring-opening, our initial focus was on optimizing the nucleophilic opening of (*S*)-*N*-(*p*-nitrobenzenesulfonyl)-2-benzylaziridine **2a** with a resin-bound diamine, which was considered an appropriate test reaction. Resin **3** was readily prepared according to a previously described procedure.[9]

Several reaction parameters were varied, including the excess of aziridine, the temperature, the reaction time, and the solvent (Table 1). Initially, the reaction was performed at 80 °C for 30 min in 1,2-dichloroethane (DCE), changing the amine/aziridine ratio. Two equivalents of **2a** seemed to give the most satisfactory results. Next, reducing the reaction time to 15 min and varying the input of microwave (MW) energy indicated that increased temperature (entry 6 in Table 1) resulted in a lowered purity of compound **4**. Subsequently, the influence of the reaction time was studied further, and it was found that limiting the reaction time to 5 min afforded a very high purity at the expence of a somewhat lower yield. Also, the effect of the solvent was examined by comparing DCE with acetonitrile or toluene−DCE (4:1), but both purity and yields were diminished. Finally, the conditions selected for additional studies encompassed the use of 2 equiv of aziridine building blocks for 5 min at 60 °C in DCE.

Similarly, MW-assisted ring-opening using resin-bound amine **3** with building blocks **2d–f** afforded compounds **7–9**, respectively, in moderate to low yields (entries 1–3 in Table 2). It was found that aziridines more sterically congested than the benzyl-substituted building block gave rise to decreased purities due to a more extensive formation of byproducts.

Moreover, a possible chain-length dependence on regioselectivity and reactivity was examined (entries 4–6 in Table 2). Thus, resin **5**, obtained from mono-*N*-Teoc-1,3-propanediamine and a trityl resin, provided the expected triamines **10–12** in excellent purities and high yields upon ring-opening of aziridines **2a−c**. Finally, the reactivity of a cyclic secondary amine was investigated, as resin **6** was prepared in a three-step procedure[9] and subsequently used for the ring-opening of aziridine **2a** to give piperidyl derivative **13** in excellent purity and yield (entry 7 in Table 2).

In conclusion, the developed SPS methodology appears to be sufficiently efficient and versatile for the creation of libraries of aliphatic or alicyclic triamine derivatives. Having obtained these promising results, the scope of the present protocol was further explored using resin-bound amino acids and two different linker types allowing preparation of carboxylic acids as well as amides. Glycine and proline were examined in these additional experiments.

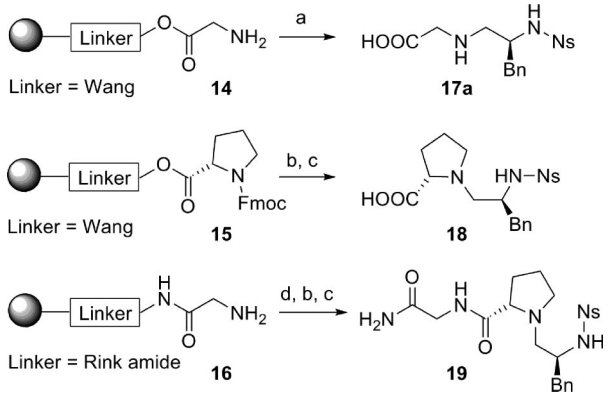
Hence, Wang resin **14** with a carboxyl-linked glycine moiety was employed in the ring-opening of aziridine **2a** to provide, after cleavage and workup, compound **17a** in excellent purity and yield (Table 3). Likewise, proline resin **15** was Fmoc-deprotected and treated with building block **2a** to give the desired proline derivative **18** in excellent purity. Moreover, dipeptide derivative **19** was prepared in high yield and purity by performing the sequence depicted in Table 3, starting from commercially available Rink amide resin **16** preloaded with a glycine moiety.

In order to compare this MW-assisted strategy with a traditional method, the ring-opening of aziridine **2a** with Wang resin **14** as nucleophile was performed at room temperature with different reaction times (5 min, 30 min, 3.5 h, and 24 h).[10] Thus, by using the amount of crude product and the initial resin loading, it was found that only ∼50% yield of glycine derivative **17a** was obtained after 3.5 h, while the yield increased to ∼85% after 24 h. Moreover, by performing this same reaction at 60

(9) Olsen, C. A.; Witt, M.; Jaroszewski, J. W.; Franzyk, H. *J. Org. Chem.* **2004**, *69*, 6149–6152.

(10) Representative procedure: To Wang resin **14** (100 mg with a loading of 0.82 mmol g^{-1}) were added successively DCE (2.2 mL) and aziridine **2a** (52 mg, 0.16 mmol, 2 equiv), and the mixture was stirred at the desired temperature for the expected time. The resin was drained and washed with DMF, MeOH, and CH_2Cl_2 (each 3 × 3 mL for 5 min) and cleaved with a solution of TFA−CH_2Cl_2 (50:50, 2 × 3 mL for 30 min), and the resulting combined solutions were coevaporated with toluene in vacuo to give the desired compound **17a**.

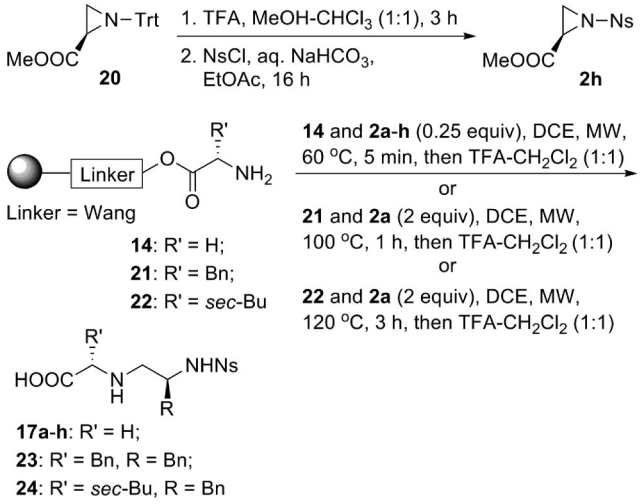
TABLE 3. MW-Assisted SPS of Glycine and Proline Derivatives 17a, 18, and 19[a]



	17a	18	19
% purity	97	97	93
% yield	>95	>95	>95

[a] Reagents and conditions: (a) **2a** (2 equiv), MW, 60 °C, 5 min, DCE, then TFA−CH_2Cl_2 (50:50); (b) 20% piperidine in DMF; (c) **2a** (2 equiv), MW, 60 °C, 5 min, DCE, then TFA−CH_2Cl_2 (95:5); (d) Fmoc-L-Pro-OH (5 equiv), PyBOP (5 equiv), HOBt (5 equiv), *i*-Pr_2EtN (10 equiv), DMF, 2 h.

SCHEME 2. Studies of Reactivities of Aziridine Building Blocks



°C, it was determined that only ∼5% and ∼75% of resin **14** were converted after 5 min and 1 h, respectively.[10,11] These results demonstrate the efficacy of the present MW-assisted SPS protocol.

With the aim to investigate the reactivity of the more hindered phenylalanine and isoleucine resins (**21** and **22**, respectively), the resins were reacted with aziridine **2a** using our established MW conditions. Expectedly, it became clear that higher reaction temperatures as well as longer reaction times were required in these cases. Thus, amino acids **23** and **24** were obtained after MW heating for 1 h at 100 °C and for 3 h at 120 °C, respectively, in good yields and with high purities (Scheme 2).[12]

Next, the relative reactivities of the aziridine building blocks were determined from a competition experiment (Scheme 2 and Figure 1), which also included aziridine ester **2h** that was prepared from the trityl ester **20** in a two-step procedure.[5] Thus, a mixture of aziridines **2a**−**h** (0.25 equiv of each) was employed in a single semipreparative reaction with resin **14** to afford glycine derivatives **17a**−**h** (Scheme 2). Analysis by HPLC−DAD and HPLC−MS[13] identified the products.[14,15] This showed that aziridine ester **2h**, as expected (due to electronic effects), exhibited a very high reactivity as compared to the remaining aziridines. Identification of the isomeric *i*-Bu- and *t*-Bu-substituted products was made by comparison with the chromatograms obtained by reacting each aziridine separately with **14**. According to this competition experiment, the tested aziridine building blocks may be grouped into (i) extremely reactive (i.e., R = CO_2Me), (ii) reactive (R = Ph, Me and Bn), and (iii) less reactive (R = *i*-Pr, *i*-Bu, *t*-Bu, and CH_2cHex). Steric hindrance explains this reactivity order, except for the two aziridines that are activated by either Ph or CO_2Me, which also gave rise to formation of regioisomers arising from nucleophilic attack at C-2, to yield **25** and **26**, respectively.

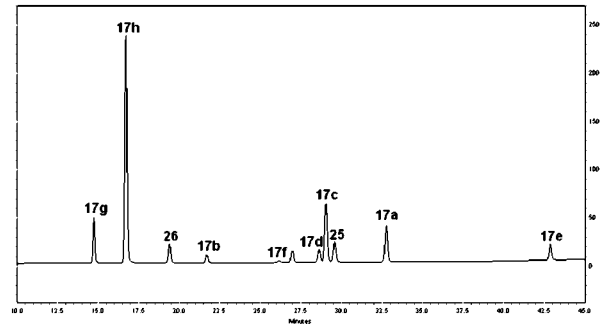


FIGURE 1. HPLC chromatogram (254 nm) of the reaction products from the MW-assisted competition experiment.[16]

In summary, an efficient MW-assisted protocol for ring-opening of activated aziridines by resin-bound amine nucleophiles has been developed, providing access to aliphatic and alicyclic polyamines as well as amino acid and peptide derivatives in moderate to high yields with excellent purities.[17] The work presented here will enable construction of new polyamine scaffolds suitable for application in medicinal chemistry, as well as novel types of peptide modification.

Experimental Section

General Methods. Microwave-assisted synthesis was carried out in a Biotage Initiator (Biotage AB, Uppsala, Sweden) apparatus operating in single mode (with irradiation at 2.45 GHz). The reactions were run in sealed vessels (0.5–2.0 mL) with magnetic stirring and a fixed hold time using variable power to reach (during 1–2 min) and then maintain the desired temperature in the vessel for the programmed time period. The temperature was monitored by an IR sensor focused on a point on the reactor vial glass. The IR sensor was calibrated to internal solution reaction temperature by the manufacturer.

Solid-phase reactions were performed in Teflon filter vessels on a control temperature heating block. Preparative HPLC separations

(11) The percentage of ring-opening conversion of resin **14** was estimated by ^{1}H NMR of the obtained crude material.

(12) Compound **23** was isolated with a >85% yield and a 93% purity. Compound **24** was isolated with ∼70% yield and a 93% purity (∼30% of the starting material was recovered also).

(13) Clarkson, C.; Stærk, D.; Hansen, S. H.; Smith, P. J.; Jaroszewski, J. W. *J. Nat. Prod.* **2006**, *69*, 1280–1288.

(14) The mass spectra of all glycine derivatives (including regioisomers) were obtained by HPLC−MS analysis. In each case, a [M − 46] peak was detected, corresponding to the loss of the nitro group of the nosyl moiety.

(15) The molecular ion peak in HPLC−MS of the unknown product with a retention time of 27.0 min (see Figure 1) was [M + H] = 179.

(16) For details of identification of each compound, see the Supporting Information.

were carried out on a 21 × 250 mm, C18 column (5 μm, 100 Å) using a system consisting of two preparative scale pumps, an autosampler, and a multiple-wavelength UV detector.

General Procedure for Synthesis of Aziridine Building Blocks 2a−g. Method A. To a cooled solution (0 °C) of the 1,2-amino alcohol **1a−g** in dry CH_2Cl_2−pyridine (2:1, 24 mL) was added *p*-nitrobenzenesulfonyl chloride (3 equiv) in one portion. Then the mixture was stirred for 5 h at room temperature. Workup as previously described by Farràs and co-workers[7] gave a crude material, which was purified by column chromatography on silica gel (using hexane−EtOAc or heptane−EtOAc mixtures as eluents). Subsequent trituration with petroleum ether afforded the desired pure aziridines **2a−g**.

Method B. The reaction was carried out as described in method A, but prior to addition of *p*-nitrobenzenesulfonyl chloride, Et_3N (1 equiv) was added at room temperature, and the mixture was stirred 30 min.

(*S*)-*N*-*p*-Nitrobenzenesulfonyl-2-cyclohexylmethylaziridine (2e): mp 107–109 °C; $[\alpha]_D = -10.8$ ($c = 4.0$ in MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (d, $J = 8.8$ Hz, 2H), 8.16 (d, $J = 8.8$ Hz, 2H), 2.88–2.99 (m, 1H), 2.75 (d, $J = 7.0$ Hz, 1H), 2.12 (d, $J = 4.7$ Hz, 1H), 1.30–1.75 (m, 5H), 0.78–1.40 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.9, 144.5, 129.6 (2C), 124.6 (2C), 40.4, 39.5, 36.7, 35.3, 33.8, 33.1, 26.7, 26.6, 26.5; HRMS (*m*/*z*) $[M + H]^+$ calcd for $[C_{15}H_{21}N_2O_4S]^+$ 325.12220, found 325.12171; ΔM, 0.2 ppm. Anal. Calcd for $C_{15}H_{20}N_2O_4S$: C, 55.54; H, 6.21; N, 8.64; S, 9.88. Found: C, 55.58; H, 6.18; N, 8.77; S, 9.67.

(17) In contrast to other sulfonamide activating groups, the nosyl group may be removed under mild conditions compatible with SPS protocols; see: Olsen, C. A.; Witt, M.; Jaroszewski, J. W.; Franzyk, H. *Synlett* **2004**, 473–476, and references cited herein.

General Procedure for MW-Assisted Ring-Opening of Aziridines. To the resin and aziridine (2 equiv) was added 1,2-dichloroethane (1 mL), and then the mixture was heated to 60 °C (or other temperature as required) under MW irradiation for 5 min (or longer depending on the substrate). The resin was drained, washed with DMF, MeOH, and CH_2Cl_2 (each 3 × 3 mL for 5 min), and then cleaved with TFA−CH_2Cl_2 (20:80 for a trityl resin, 50:50 for a Wang resin and 95:5 for a Rink amide resin, 2 × 3 mL, each for 30 min), and the resulting combined solutions were coevaporated with toluene in vacuo to give the desired compound.

***N*-{(1*S*)-2-[(6-Aminohexyl)amino]-1-benzylethyl}-4-nitrobenzenesulfonamide (4):** ^{1}H NMR (300 MHz, CD_3OD) δ 8.25 (d, $J = 9.1$ Hz, 2H), 7.88 (d, $J = 9.1$ Hz, 2H), 7.04–7.17 (m, 5H), 3.83–4.05 (m, 1H), 3.20–3.42 (m, 4H), 3.11 (t, $J = 7.6$ Hz, 2H), 2.96 (dd, $J = 14.1$ Hz and $J = 4.7$ Hz, 1H), 2.62 (dd, $J = 14.1$ Hz and $J = 10.0$ Hz, 1H), 1.78–2.03 (m, 4H), 1.58–1.70 (m, 4H); ^{13}C NMR (75 MHz, CD_3OD) δ 151.0, 146.7, 137.2, 130.1 (2C), 129.4 (2C), 129.0 (2C), 127.6, 125.2 (2C), 54.5, 53.7, 49.5, 40.5, 39.1, 28.4, 27.1, 27.0, 26.9; HRMS (*m*/*z*) $[M + H]^+$ calcd for $[C_{21}H_{31}N_4O_4S]^+$ 435.20605, found 435.20596; ΔM, 0.2 ppm.

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Supporting Information Available: Materials, full experimental procedures, crystal structure data, and compound characterization data including ^{1}H and/or ^{13}C NMR spectra for all compounds from preparative experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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