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The Dinosyl Group: A Powerful Activator for the Regioselective Alcoholysis of Aziridines

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The *N*-2,4-dinitrophenylsulfonyl group (dinosyl, DNs) was found to be an excellent choice for the N-activation of aziridines towards ring cleavage with primary, secondary, and sterically demanding tertiary alcohols. Alcoholysis does not need any additional catalyst and is regioselective for the less-hindered position. No racemization in the aziridine formation or cleavage step was observed, and the resulting DNs-sulfonamides can be deprotected quantitatively under mild conditions.

Introduction

N-Activated aziridines are versatile synthetic intermediates[1–3] (e.g., several syntheses of Oseltamivir[4]) and easily accessible from amino alcohols,[5–9] from carbene attack on imines (aza-Darzens reaction),[10] or by direct aziridination of alkenes.[11–14] Although aziridines are close analogs to epoxides, substitution at the nitrogen atom offers an additional handle for tuning their reactivity. Among a large variety of possible activating groups, sulfonyl and in particular tosyl activation is widely used, for good reasons. *N*-Ts-Aziridines exhibit relatively high reactivity towards ring cleavage and they do not undergo side reactions at the activating group, which is observed with *N*-acyl- or carbamate-type aziridines.[15,16] In our research towards new synthetic ligands for the polyamine binding site of the NMDA receptor[17–19] we encountered difficulties in the synthesis of compound **B**, intended as a prototype for a combinatorial library of compounds with general structure **A** (Figure 1).

We considered nucleophilic ring opening of an activated 2-benzylaziridine with a corresponding alcohol intermediate as a short and elegant solution for this synthetic problem. While sufficiently activated aziridines undergo ring cleavage with a variety of strong nucleophiles[16,20] easily, weak nucleophiles like alcohols generally require either the application of the corresponding alkoxide[15,21–25] or, more frequently, the use of Lewis acids as catalysts.[26–32] Only few sporadically mentioned examples of uncatalyzed alcoholysis (MeOH, EtOH) of aziridines are reported.[15,21,25,33] Addressing this, we were striving for easily accessible N-activated aziridines that are reactive enough to undergo regioselective alcoholysis without any additional activation. *N*-Ts-Aziridines were considered as an obvious starting point, although ring cleavage with weak nucleophiles like alcohols in general still requires additional activation. However, several publications have underlined the increased reactivity of 2- or 4-nitrophenylsulfonylaziridines (Nosyl, Ns) with strong nucleophiles compared to Ts-aziridines,[21,34,35] and very recently the cleavage of Ns-aziridines with phenolates was described.[36]

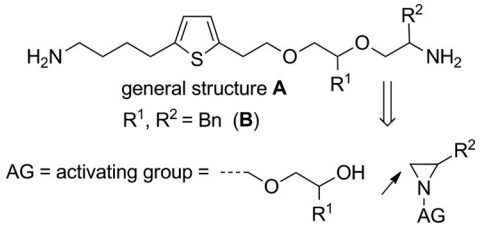

Figure 1. Envisioned synthetic strategy towards structure **A**.

We were optimistic that the formal addition of a second nitro group leading to 2,4-dinitrophenylsulfonylaziridines (Dinosyl, DNs) should sufficiently activate the ring system to allow catalyst-free alcoholysis under neutral conditions, even with sterically demanding alcohols (Figure 2). Furthermore, mild and high-yielding deprotection methods based on S nucleophiles are already established for the DNs-sulfonamide moiety.[37–39] This represents another advantage over Ts activation leading to sulfonamides, which are very stable compounds that require harsh deprotection conditions like *mischmetal*/$TiCl_4$[40] or SmI_2/amine/water[41] – to mention only the milder and more modern methodologies – thus significantly limiting functional group tolerance.

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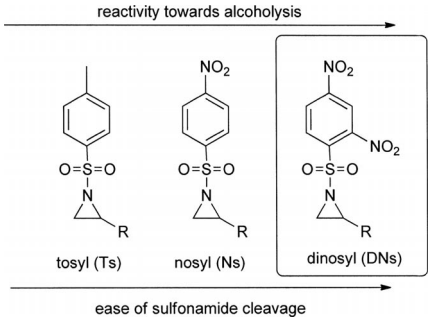
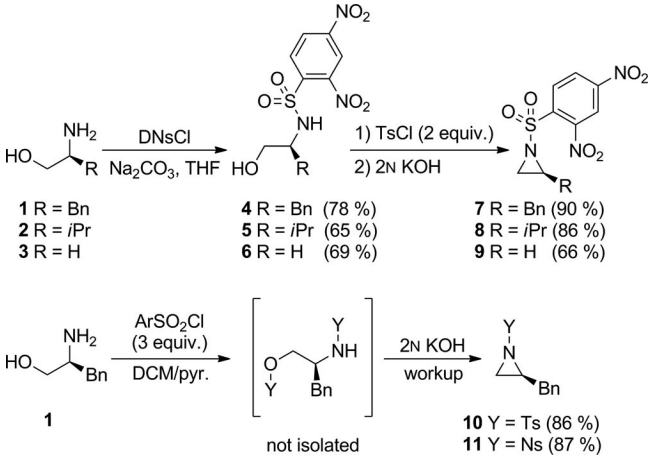


Figure 2. Comparison of the dinosyl, nosyl,-and tosyl groups.

Results and Discussion

An initial proof of concept experiment was designed utilizing 2-benzylaziridine as an example, which was synthesized with Ts, Ns, and DNs activation to allow comparison of reactivity. Known *N*-Ts- and *N*-Ns-aziridines **10**[41] and **11**[42] were prepared starting from phenylalaninol (**1**) through a simple one-pot procedure involving sulfonylation with an excess amount of TsCl/NsCl followed by treatment with aqueous KOH during workup.[42] For the preparation of DNs-aziridine **7**, a two-step protocol was established. Initial equimolar *N*-dinosylation through an adapted tosylation protocol[43] to give sulfonamide **4** was followed by ring closure with an excess amount of TsCl (Scheme 1). This two-step process allows to save on the more-expensive DNsCl.

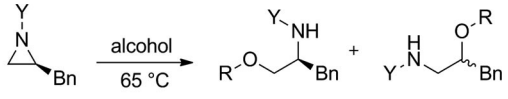


Scheme 1. Synthesis of DNs-, Ns-, and Ts-aziridines **7**–**11**.

The first alcoholysis experiments were conducted with 2-Bn-DNs-aziridine **7** in MeOH as potentially the most reactive alcohol. Already at room temperature, conversion of the starting material was observed at a low reaction rate. By raising the temperature to 65 °C, fast and complete conversion of **7** was achieved within several hours. The observed ratio between the two possible regioisomers was in clear favor of the product related to attack at the unsubstituted carbon center (i.e., **12a**, normal product) and against attack at the substituted carbon (i.e., **12b**, abnormal product). No other byproducts were observed. Consequently, DNs-aziridine **7** and analogous Ns- and Ts-aziridines **11** and **10** were treated under identical conditions with a variety of alcohols (primary to tertiary) with HPLC monitoring.

Representative results are compiled in Table 1, which underline the superiority of the DNs activation with respect to reactivity and site specificity. While DNs-aziridine **7** was quickly cleaved by *t*BuOH in quantitative yield and without formation of any byproducts, Ns-aziridine **11** needed a substantially longer reaction time. Conversion of Ts-aziridine **10** reached completion only with MeOH (**18a**,[44] within 8 d), whereas only incomplete formation of **19a/19b** was achieved with *i*PrOH. In all experiments the regioselectivity was in clear favor of the normal product (^{1}H NMR spectroscopic analysis of crude materials).

Table 1. DNs activation vs. Ns and Ts activation.



Entry	Substrate	Y	Alcohol	Target	Time [h]	**a/b**[a]
1	**7**	DNs	MeOH	**12a**	7	95:5
2	**7**	DNs	BnOH	**13a**	7	92:8
3	**7**	DNs	*i*PrOH	**14a**	7	96:4
4	**7**	DNs	*t*BuOH	**15a**	7	>99:1[b]
5	**11**	Ns	*i*PrOH	**16a**	72	94:6
6	**11**	Ns	*t*BuOH	**17a**	96	>99:1[b]
7	**10**	Ts	MeOH	**18a**	192	85:15
8	**10**	Ts	*i*PrOH	**19a**	incompl.[c]	93:7

[a] According to ^{1}H NMR spectroscopic analysis of the crude material. [b] No minor compound was observed by HPLC or ^{1}H NMR spectroscopy. [c] Stopped at 80% conversion after 22 d at 65 °C.

It is noteworthy that DNs-aziridine **7** has a lower solubility in the used alcohols than **10** and **11**. In diluted solutions, the superiority of DNs activation is even more pronounced, which was demonstrated for alcoholysis of **7**, **10**, and **11** in *i*PrOH at 0.1% concentration (Figure 3).

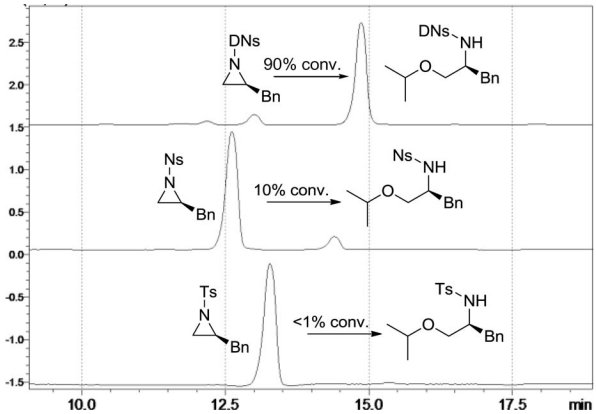
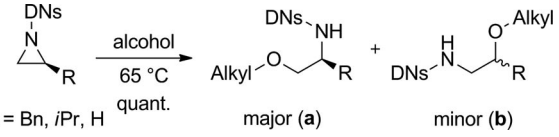


Figure 3. Alcoholysis of **7**, **10**, and **11** in 0.1% dry *i*PrOH (HPLC).

For a systematic evaluation of DNs activation, two additional DNs-aziridines (2-isopropylaziridine **8** and parent compound **9**) were prepared analogously to **7** (Scheme 1). To evaluate the influence of steric demand of the C2 substituent on the reaction rate and regioselectivity, **8** and **9** were treated with selected alcohols under the same conditions (5%; 65 °C) as those used for **7** (Table 2), including two examples from Table 1). In all experiments clean and complete conversion was observed within a reasonable amount of time and the regioselectivity for the normal product was high (Table 2). However, two conclusions can be drawn from the obtained data. First, the regioselectivity towards the normal product increases with increasing steric demand of the alcohol (both series). Second, aziridine **8** (R = *i*Pr) requires prolonged reaction times and shows slightly lower regioselectivity than 2-benzylaziridine **7** independent of the applied alcohol. Following this trend, aziridine **9** showed the fastest conversion, although this effect was only observable under more dilute conditions due to the extremely low solubility of **9**. For all reported experiments the major regioisomers (normal products) were isolated in pure form either by recrystallization or by silica gel chromatography.

Table 2. Comparative alcoholysis of DNs-aziridines **7**, **8**, and **9**.



Entry	Substrate	R	Alcohol	Target	Time [h]	**a/b**[a]
1	**7**	Bn	MeOH	**12a**	7	95:5
2	**7**	Bn	*t*BuOH	**15a**	7	>99:1[b]
3	**8**	*i*Pr	MeOH	**20a**	17	87:13
4	**8**	*i*Pr	BnOH	**21a**	65	88:12
5	**8**	*i*Pr	*i*PrOH	**22a**	40	92:8
6	**8**	*i*Pr	*t*BuOH	**23a**	60	>99:1[b]
7	**9**	H	MeOH	**24**	<2[c]	single isomers
8	**9**	H	BnOH	**25**	<3[c]	
9	**9**	H	*i*PrOH	**26**	<3[c]	
10	**9**	H	*t*BuOH	**27**	<3[c]	

[a] According to ^{1}H NMR spectroscopic analysis of the crude material. [b] No minor compound was observed by HPLC or ^{1}H NMR spectroscopy. [c] Due to very low solubility of **9**, data is from 2 mg/mL experiment.

DNs-Aziridines **7** and **8** used so far were prepared from optically pure (*S*)-amino alcohols. In order to investigate possible racemization during the formation and ring-cleavage process, smaller amounts of racemic (*R*/*S*)-**7** and **8** were prepared and submitted to selected alcoholysis experiments. These racemic materials were then analyzed by chiral HPLC analysis. For compound **23a**, baseline separation of the two enantiomers was achieved (Figure 4). To further support ring cleavage without racemization, DNs-sulfonamides **12a** and **16a** were selected for deprotection based on a literature protocol[39] (Scheme 2).

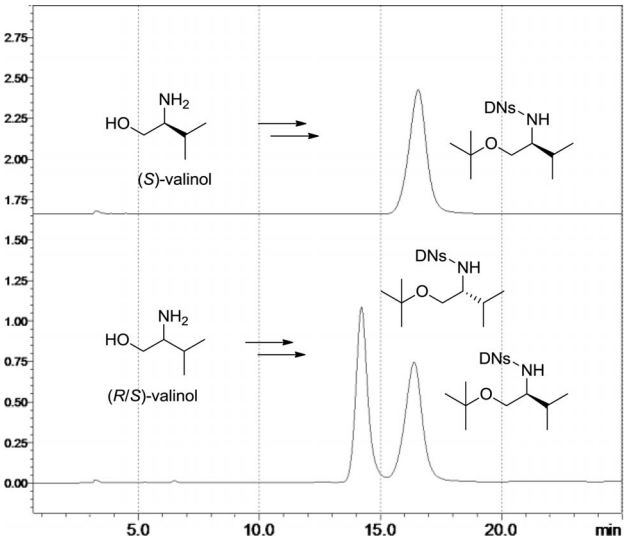
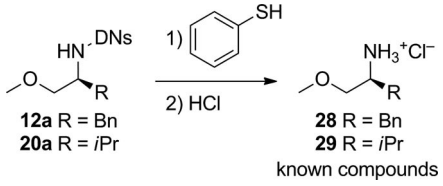


Figure 4. Chiral HPLC from racemic and enantiopure **23a**.



Scheme 2. Deprotection and proof of structure.

Deprotection was fast and high yielding using thiophenol (2 equiv.) in DCM/DMF (99:1). The products were purified by column chromatography, and the amino ethers were converted into the hydrochloride salts and recrystallized to give pure **28** and **29**, which are known compounds. Their physical data were consistent with the literature,[45] thus supporting that also racemization did not occur during cleavage of the DNs group.

Conclusions

In conclusion, the *N*-2,4-dinitrophenylsulfonyl (Dinosyl, DNs) group was found to be the most potent activator for the uncatalyzed alcoholysis of aziridines up to date. The newly prepared DNs-aziridines are shelf stable and readily available from the corresponding amino alcohols in enantiopure form. They undergo uncatalyzed alcoholysis with primary, secondary, and tertiary alcohols, exhibiting complete and byproduct-free conversion and high selectivity for the cleavage at the sterically less-hindered carbon center. It was shown that no racemization occurred during aziridine formation and alcoholysis (chiral HPLC) under the conditions applied. The resulting DNs-sulfonamides are shelf stable compounds as well and allow further N-decoration (alkylation,[37,38] Mitsunobu-type[37,38,46–49] or Pd-cata-

lyzed transformations[50,51]) with subsequent deprotection[37,46] or immediate deprotection[39] to the primary amine, which was demonstrated for two selected examples. Currently, the methodology of the DNs-mediated alcoholysis is expanded towards more valuable alcohols that cannot be applied as solvents in excess amounts. Therefore, appropriate co-solvents are being evaluated and transfer to microwave- and flow-conditions is under investigation. The successful implementation of this new methodology to the initial research problem will be reported together with the corresponding pharmacological data.

Experimental Section

Representative Procedure for the Alcoholysis of DNs-Aziridines 7–9

(*S*)-*N*-[1-Benzyl-2-(1-methylethoxy)ethyl]-2,4-dinitrophenylsulfonamide (14a): Dry *i*PrOH (4 mL) was added to 2-benzylaziridine (**7**; 215 mg, 0.592 mmol), and the mixture was stirred in closed Pyrex glassware at 65 °C external temperature under HPLC monitoring. Evaporation and analysis (^{1}H NMR spectroscopy) of the crude material indicated complete conversion to diastereomers **14a/14b** in a ratio of 96:4. Recrystallization (Et_2O/hexane) gave pure **14a** (200 mg, 80%) as white crystals. M.p. 106–107 °C (MTBE). HPLC: t_R = 12.99 min. $[\alpha]_D^{20}$ = +55 (c = 1.0, $CHCl_3$). $C_{18}H_{21}N_3O_7S$ (423.45): calcd. C 51.06, H 5.00, N 9.92, S 7.57; found C 51.05, H 5.02, N 9.88, S 6.37. IR (KBr): $\tilde{\nu}$ = 3369, 3091, 2965, 2876, 1610, 1551, 1426, 1367, 1348, 1168, 1080, 912, 839, 816, 747 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.07 (d, J = 6.1 Hz, 3 H, CH_3), 1.09 (d, J = 6.1 Hz, 3 H, CH_3), 2.77 (dd, J = 14.0, 8.4 Hz, 1 H, PhC*H*H), 2.95 (dd, J = 13.9, 6.2 Hz, 1 H, PhCH*H*), 3.30–3.62 (m, 3 H, OCH_2, OCH), 3.72–3.94 (m, 1 H, NCH), 5.75 (d, J = 8.1 Hz, 1 H, NH), 6.95–7.15 (m, 5 H, 5 PhH), 8.05 (d, J = 8.6 Hz, 1 H, DNs-H6), 8.35 (dd, J = 8.7, 2.1 Hz, 1 H, DNs-H5), 8.55 (d, J = 2.0 Hz, 1 H, DNs-H3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.8 (q, CH_3), 21.9 (q, CH_3), 38.8 (t, $PhCH_2$), 57.5 (d, NCH), 69.6 (t, OCH_2), 72.3 (d, OCH), 120.6 (d, DNs-C3), 126.6, 127.1 (2 d, PhC4, DNs-C5), 128.4 (d, PhC3/5), 129.3 (d, PhC2/6), 131.8 (d, DNs-C6), 137.2 (s, PhC1), 140.1 (s, DNs-C), 147.3 (s, DNs-C), 149.3 (s, DNs-C) ppm. MS (ESI): m/z = 422 [M – H]$^-$, 358 [M – SO_2 – H]$^-$.

Supporting Information (see footnote on the first page of this article): Experimental details for the preparation and characterization (including ^{1}H and ^{13}C NMR spectra) of all new compounds.

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