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Ring opening of aziridines with tetranitromethane in the presence of triethylamine. Efficient synthesis of β-tosylamino nitrates

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ABSTRACT

A convenient method for the preparation of β-tosylamino nitrates based on the ring-opening reaction of aziridines by tetranitromethane in the presence of triethylamine is described. A series of substituted β-amino nitrates is obtained in high yields under mild conditions.

Organic nitrates are known to be nitric oxide (NO) releasing and several examples have been used as drugs in clinical practice for over a century.[1] In the last 20 years intense efforts were made by chemists towards new chemical entities, combining well-known drugs with an NO-donating moiety, and obtaining products which have found widespread applications in cardiovascular pharmacology, immunology and neurobiology.[2] Aminoalkyl nitrates, including β-amino nitrates, were utilized as nitrate tethers to modify known drug molecules.[3] Also, the combination of a nitrooxy group with an alkylamino fragment was used for the design of many explosives.[4,5] Therefore, the development of new and efficient approaches to amino nitrates and their derivatives has attracted significant attention.

The preparation of amino nitrates is generally accomplished by two methods: esterification of an appropriate amino alcohol[3b,6] and reaction of a suitable amino alkyl halide with silver nitrate.[3a,6a,7] However, these methods are unsuitable for large-scale application owing to some limitations: they require strong acidic conditions or large amounts of expensive reagents. Other methods were used in a few instances. Recently, a few improved methods for the synthesis of β-amino nitrates based on the ring-opening reactions of aziridines with nitric oxide[8] or bismuth[9] and zirconyl[10] nitrates as the source of nitrate ions were published.

In this Letter we report a new and simple synthesis of β-tosylamino nitrates via *N*-tosylaziridine opening with tetranitromethane (TNM) in the presence of triethylamine. Previously, we found that TNM–Et_3N could be utilized for the efficient ring opening of epoxides to give β-hydroxy nitrates.[11] In continuation of our investigations on the reactivity of TNM–Et_3N towards three-membered heterocycles we studied the reactions of substituted aziridines, *N*-tosylaziridines **1a–h**, with TNM in the presence of triethylamine.

The starting *N*-tosylaziridines **1a–h** were prepared via a known procedure.[12] At first we carried out a brief survey to optimize the aziridine opening conditions for model heterocycle **1a**. A screen of solvents and reaction temperatures indicated that stirring the reaction mixture in dioxane at 20 °C for three days (procedure A)[13] led to a clean reaction and a good isolated yield (65%) of **2a** (Table 1, entry 1). The use of microwave irradiation (procedure B)[13] was also demonstrated; the product **2a** was obtained in 71% yield in 2 h (Table 1, entry 2).

The optimized reaction conditions (TNM–Et_3N, dioxane, 20 °C or microwave-assisted reaction) were successfully applied to a variety of alkyl and aryl substituted aziridines **1a–h** to provide β-nitrooxy sulfonamides **2a–d** or **3c–h** in high yields.[13] The results obtained are summarized in Table 1. Symmetrical aziridines **1a**,**b** (Table 1, entries 1–3) afforded β-tosylamino nitrates **2a**,**b** as single diastereomers. It is known that fused bicyclic aziridine ring opening proceeds via attack of the nucleophile on the three-membered ring to give the product with trans configuration.[14] The structure of **2a** was identified by X-ray crystallography (Fig. 1, CCDC-738539) and shows that the product adopts a trans-diequatorial conformation.

The reactions of alkyl-substituted unsymmetrical aziridines **1c** and **1d** with TNM–Et_3N led to a mixture of two regioisomers **2c**/**3c** and **2d**/**3d** in a 65:35 ratio in each case (Table 1, entries 4–6). In both products the primary nitrates **2c** and **2d** prevailed over the secondary nitrates **3c** and **3d**. The ring opening of aziridines **1e–h** occurred with excellent regioselectivity. 1-Azaspiro[2.3]hex-

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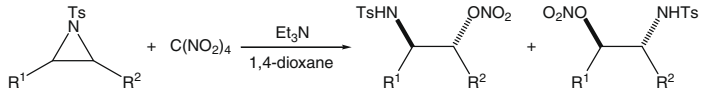
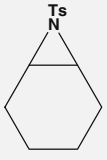
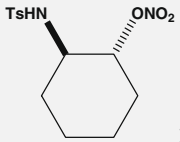
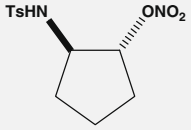
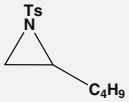
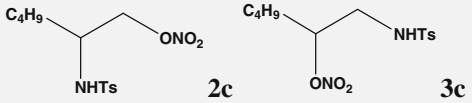
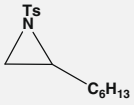
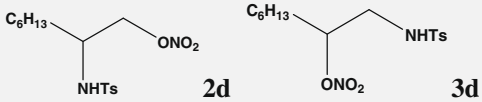
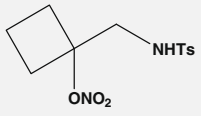
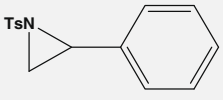
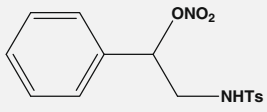
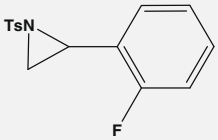
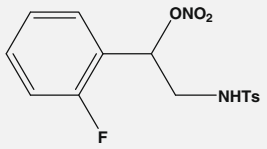
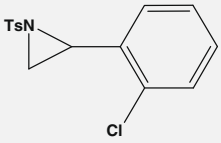
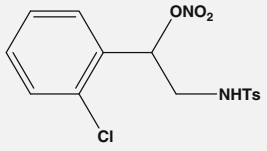
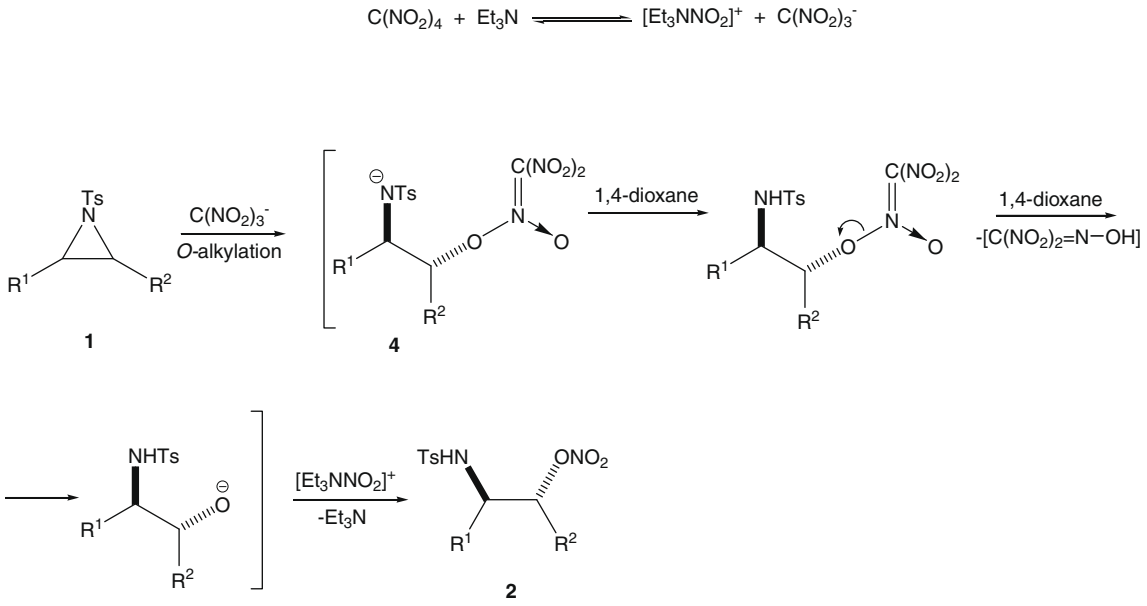
Table 1
Reactions of *N*-tosylaziridines with tetranitromethane in the presence of triethylamine



Entry	Aziridine **1**	Conditions[13]	Time	β-Tosylamino nitrate **2**, **3**	Yield **2**, **3** (%)
1	 **1a**	A	3 d	 **2a**	65
2		B	2 h		71
3	 **1b**	A	14 d	 **2b**	52
4	 **1c**	A	14 d	 **2c** **3c**	79[a]
				2c/3c = 65/35	
5	 **1d**	A	14 d	 **2d** **3d**	65[a]
6		B	2 h		61
				2d/3d = 65/35	
7	 **1e**	A	14 d	 **3e**	50
8	 **1f**	A	5 d	 **3f**	68
9	 **1g**	A	14 d	 **3g**	67
10		B	2 h		63
11	 **1h**	A	14 d	 **3h**	62

[a] The ratio of regioisomers was determined by ^{1}H NMR spectroscopy. Combined yield of both isomers.



Scheme 1.

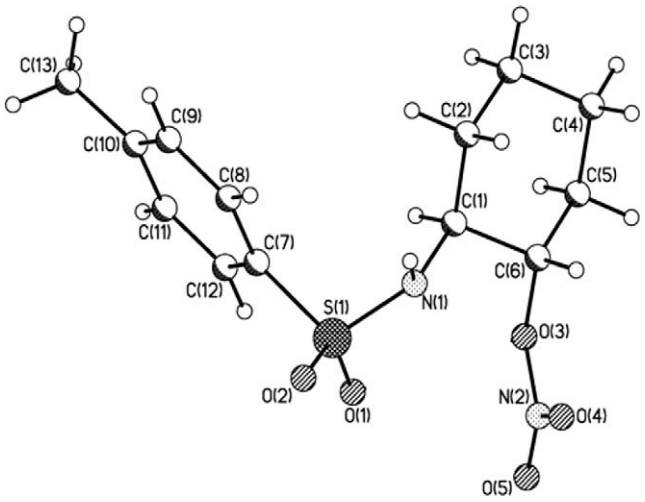


Figure 1. X-ray crystal structure of compound **2a** (SHELXTL PLUS).

ane tosylamide **1e** and 2-aryl aziridines **1f–h** afforded only the products **3e–h** as a result of ring cleavage at the more substituted 3-position (Table 1, entries 7–11), in contrast to monoalkyl-substituted aziridines **1c**,**d**. The high regioselectivity observed in the reactions of aziridines **1e–h** with TNM–Et_3N may be explained by electronic factors. There is preference for nucleophilic attack at the carbon atom which can better accommodate a positive charge in the transition state.[15] The structures of all the synthesized nitrates were unequivocally established by ^1H and ^{13}C NMR spectroscopy and elemental analysis.

The mechanism of this reaction requires further investigation. According to the literature, nucleophilic opening of *N*-tosyl-substituted aziridines[15] and oxiranes[11] can proceed via the pathway presented in Scheme 1. We assume that the key step of the reaction is O-alkylation of aziridines **1** by the trinitromethyl anion to give unstable nitronates **4** which are transformed into β-tosylamino nitrates **2** after solvolysis and nitration. Presumably, the source of the proton in the final tosylamino nitrates is 1,4-dioxane.[16] It is necessary to employ TNM combined with triethylamine to produce the nucleophilic species $(O_2N)_3C^-$ that reacts with the aziridines.

In summary we have developed a preparative and efficient synthesis of β-tosylamino nitrates which are of potential synthetic and pharmacological interest. High regioselectivity, good yields of final products, the simplicity of procedure and the ready availability of the starting reagents are the main advantages of this method making it an interesting alternative to other β-tosylamino nitrate syntheses.

Caution: Although we did not experience any problems in handling these compounds, full safety precautions should be taken due to their potentially explosive nature.

Acknowledgements

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13. *General procedure A*: Triethylamine (0.14 ml, 1 mmol) was added gradually at 5 °C to a solution of TNM (0.22 ml, 2 mmol) in 1,4-dioxane (2 ml). The mixture was stirred for 5 min with cooling, after which the corresponding aziridine (1 mmol) was added. The resulting mixture was stirred at room temperature for the specified time according to Table 1. TLC and NMR spectra were used to monitor the progress of the reactions. On completion, the solvent was evaporated and the product was isolated by column chromatography (hexane–ethyl acetate, 4:1).
General procedure B: The procedure was carried out as described above using a CEM-discover monomode system. The reaction mixture was placed into a microwave vessel (10 ml) containing a Teflon-coated magnetic stirrer bar. The sample was irradiated for 2 h. For safety, the maximum power was set to 10 W and the maximum temperature was set to 50 °C. On completion, the solvent was evaporated and the product was isolated by column chromatography (hexane–ethyl acetate, 4:1).
Spectral and analytical data of representative products:
1-[(4-Methylphenylsulfonamido)methyl]cyclobutyl nitrate (**3e**). Pale yellow solid; mp = 87–89 °C; R_f 0.40 (hexane–ethyl acetate, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.69–1.84 (m, 1H, CH_2), 1.93–2.04 (m, 1H, CH_2), 2.25–2.37 (m, 4H, CH_2), 2.45 (s, 3H, CH_3), 3.47 (d, ^3J = 6.7 Hz, 2H, CH_2NH), 5.14 (br t, ^3J = 6.7 Hz, 1H, NH), 7.33 (d, ^3J = 8.2 Hz, 2H, 2 × CH), 7.76 (d, ^3J = 8.2 Hz, 2H, 2 × CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.3 (CH_2), 21.5 (CH_3), 30.3 (2 × CH_2), 45.5 (CH_2NH), 86.8 ($CONO_2$), 127.0 (2 × CH, Ph), 129.9 (2 × CH, Ph), 136.8, 143.8 (C); IR (KBr): ν_{max} 3297 (w, br), 1627 (s), 1427 (s), 1307 (s) cm^{-1}; Anal. Calcd for $C_{12}H_{16}N_2O_5S$: C, 47.99; H, 5.37; N, 9.33. Found: C, 47.55; H, 5.14; N, 9.31.
1-(2-Fluorophenyl)-2-(4-methylphenylsulfonamido)ethyl nitrate (**3g**). Yellow oil; R_f 0.53 (hexane–ethyl acetate, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.44 (s, 3H, CH_3), 3.35–3.54 (m, 2H, CH_2NH), 5.16–5.23 (m, 1H, NH), 6.10 (dd, ^3J = 4.1, 8.6 Hz, 1H, $CHONO_2$), 7.06–7.17 (m, 2H), 7.27–7.37 (m, 2H), 7.31 (d, ^3J = 8.3 Hz, 2H, 2 × CH), 7.77 (d, ^3J = 8.3 Hz, 2H, 2 × CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.6 (CH_3), 44.8 (CH_2NH), 77.7 ($CHONO_2$), 116.1 (d, J = 21.0 Hz, CH), 122.1 (d, J = 13.3 Hz, C), 124.8 (CH), 127.0 (2 × CH), 127.6 (CH), 130.0 (2 × CH), 131.3 (CH), 136.8 (C), 144.0 (C), 160.1 (d, J = 249.6 Hz, C); IR (KBr): ν_{max} 3280 (w, br), 1643 (s), 1455 (s), 1330 (s) cm^{-1}; Anal. Calcd for $C_{15}H_{15}FN_2O_5S$: C, 50.84; H, 4.27; N, 7.91. Found: C, 50.65; H, 4.07; N, 7.77.
1-(2-Chlorophenyl)-2-(4-methylphenylsulfonamido)ethyl nitrate (**3h**). Yellow oil; R_f 0.49 (hexane–ethyl acetate, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.45 (s, 3H, CH_3), 3.28–3.43 (m, 2H, CH_2NH), 5.27 (br dd, ^3J = 5.7, 7.5 Hz, 1H, NH), 5.80 (dd, ^3J = 4.5, 8.5 Hz, 1H, $CHONO_2$), 7.15–7.34 (m, 6H), 7.73 (d, ^3J = 8.1 Hz, 2H, 2 × CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.6 (CH_3), 45.8 (CH_2NH), 82.6 ($CHONO_2$), 124.7, 126.6 (CH, Ph), 127.0 (2 × CH, Ph), 129.9 (CH, Ph), 130.0 (2 × CH, Ph), 130.5 (CH), 135.1 (C), 136.6 (C), 136.7 (C), 144.2 (C); IR (KBr): ν_{max} 3280 (w, br), 1643 (s), 1477 (s), 1330 (s) cm^{-1}; Anal. Calcd for $C_{15}H_{15}ClN_2O_5S$: C, 48.59; H, 4.08; N, 7.55. Found: C, 48.75; H, 4.09; N, 7.39.
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16. In the NMR spectra of the reaction mixtures of the aziridines with TNM–Et_3N, we observed signals which presumably can be attributed to mononitro substituted 1,4-dioxane. An analogous process was identified in our previous work using THF.[17]
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