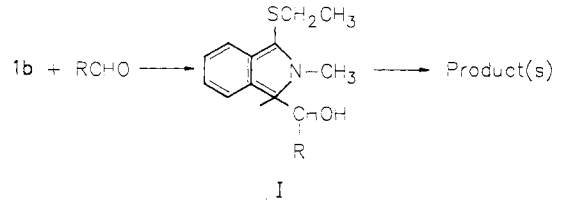
Scheme II



I

Our interpretation of these observations is summarized in Schemes I and II for isoindoles of type **1a** and **1b**, respectively. In both cases, the sequence is initiated by attack of the aldehyde at C(3) of the isoindole ring. For isoindoles such as **1a** this results in formation of the rapidly hydrolyzed **4** (nonelectroactive) and ultimately **3a**. **1b** and similar isoindoles are suggested to undergo a normal substitution resulting in formation of I (the proposed electroactive intermediate), which undergoes a slower deocmposition to mixed products, probably largely polymeric.

Experimental Section

Chemicals. All thiols, amines, and aldehydes were obtained from Aldrich Chemical Co. Glass-distilled methanol and acetonitrile were from Burdick and Jackson; other solvents were J. T. Baker reagent grade. Buffer components were from J. T. Baker or Mallinkrodt (all reagent grade or better). Deionized water was prepared with a Barnstead Nanopure system.

Liquid Chromatography. Reaction mixtures were routinely monitored on a Bioanalytical Systems, Inc. LC-304 liquid chromatography fitted with a 0.46 × cm C-18 column (MF 6030). For detection, a standard TL-5A thin layer amperometric transducer operated at an applied potential of 0.75 V vs. Ag/AgCl was employed. Isoindole derivatives were chromatographed by using acetate buffered (0.1 M, pH 5) mobile phases of water/acetonitrile.

Kinetic Studies. Isoindoles were generated from stoichiometric quantities of reagents as follows: 150 μL each of 5 mM solutions of OPA, thiol, and amine were mixed and incubated 5 min at 25 °C, after which they were diluted with 5.6 mL of a solution of the corresponding aldehyde. The concentration of aldehyde was normally determined by its solubility, but in most cases represented 100–150-fold molar excess. All solutions described above were prepared in 25% methanol buffered at pH 9.6 with 0.1 M sodium carbonate. Loss of isoindole and formation of the electrochemically active intermediate were monitored by chromatographic analysis of aliquots at timed intervals. Second-order rate constants were obtained by dividing the apparent pseudo-first-order constant by [RCHO].

Formaldehyde-Promoted Degradation of 1-[(2-Hydroxyethyl)thio]-2-(1-propyl)isoindole (1c). Isoindole **1c** was generated in situ by the addition of *n*-propylamine (220 μL) to a solution of *o*-phthalaldehyde (367 mg) and 2-mercaptoethanol (210 μL) in methanol (50 mL) at 0 °C. This was then added over 35 min to a stirred solution of formaldehyde prepared by adding 10 mL of a 0.5 M sodium carbonate solution (pH 9.6) to 15 mL of methanol followed by addition of 37% formaldehyde solution to give a total volume of 50 mL (the formaldehyde solution was kept at room temperature for the duration of the addition of isoindole).

After the completion of the addition of **1c**, the solution was stirred 2 h and then kept overnight at −20 °C. Methanol was removed by evaporation and the aqueous suspension was extracted with chloroform. The chloroform extracts were combined and dried over $MgSO_4$, filtered, and evaporated to give 1.28 g of a yellow oil; 0.64 g of this material was chromatographed in three portions over silica gel (230–400 mesh, 1.5 × 30 cm column size) using CH_2Cl_2/CH_3OH (18/1, v/v) to give a white solid (148.1 mg, 53%). This was crystallized from ether–methanol (ca. 10/1, v/v) and identified as 2,3-dihydro-3-(hydroxymethyl)-2-(1-propyl)-1*H*-isoindol-1-one (**2**): mp 115–116 °C; NMR ($CDCl_3$) 7.81 (d, J = 7.1 Hz, 1), 7.53 (m, 3), 4.32 (m, 1), 4.06 (m, 2), 3.90 (m, 1), 3.29 (m, 1), 1.70 (m, 2), 1.60 (s, 1), 3.95 (t, J = 7.3 Hz, 3); IR (KBr) 3390 (OH), 2850, 2900, 2940 (CH), 1660 (amide C=O), 1410, 1045, 710, 680 cm^{-1}; CIMS (70 eV, CH_4), m/z (rel intensity) 206 (100, M + 1); high resolution mass spectrum, calcd for $C_{12}H_{15}NO_2$ 205.11027, found 205.11008.

OPA-Promoted Degradation of 1-[(2-Hydroxyethyl)thio]-2-methylisoindole (1a). A solution of **1a** was prepared at 0 °C in methanol (5 mL) from OPA (100.7 mg), 2-hydroxyethanethiol (53 μL), and methylamine (64 μL of a 40% aqueous solution). This was added over 50 min to a stirred solution of OPA (567.3 mg) in a mixture of methanol (5 mL) and 0.1 M aqueous sodium carbonate (pH 9.6, 5 mL) at room temperature. Stirring was continued 15 min and the mixture was stored at −20 °C overnight. The solid was isolated (102.1 mg, 47%). The melting range of this materal was 212–213 °C (lit.[6] mp 220–222 °C), but after recrystallization from methanol, the compound melted at 208–210 °C. Repeated recrystallization did not change this. However, TLC (4 solvent systems) behavior as well as NMR, IR, and CIMS were identical with those of an authentic sample of **3a** prepared by the literature procedure.[6]

OPA-Promoted Degradation of 1-[(2-Hydroxyethyl)thio]-2-(1-butyl)isoindole (1d). The procedure above was repeated with **1d**. The crude **3b** was isolated in 44% yield. After two recrystallizations from acetone–methanol the compound had a melting point of 176–178 °C (lit.[6] mp 177–179°C) and was identified as **3b** by comparison with an authentic sample (NMR, IR). In the formation of both **3a** and **3b** TLC showed more product present in the reaction mixture, but this was not isolated due to the large quantities of other materials present (e.g., excess OPA, minor side products).

Acknowledgment. Support of this research under the Small Business Innovative Research program of the National Institute of General Medical Sciences, National Institutes of Health, Public Health Service, is gratefully appreciated.

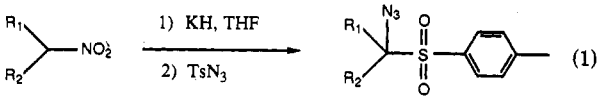
A One-Step Preparation of α-Azido Sulfones from Nitro Compounds

Emil R. Koft

Department of Chemistry, Rensselaer Polytechnic Institute, Troy, New York 12180-3590

Received February 20, 1987

Activated azides are versatile reagents for diazo group transfer to a variety of active methylene compounds[1] including α-nitro ketones and nitro esters.[2] Arenesulfonyl azides have also been noted as azide donors to organometallic nucleophiles.[3,4] We disclose in this paper an unusual reaction (eq 1) between isolated nitronates and toluenesulfonyl azide leading to the formation of α-azido sulfones **2**, a functional group combination often available only with difficulty via other methods.[5]



(1)

1 2

As shown in Table I, a preliminary survey of simple substrates revealed that this reaction is applicable to

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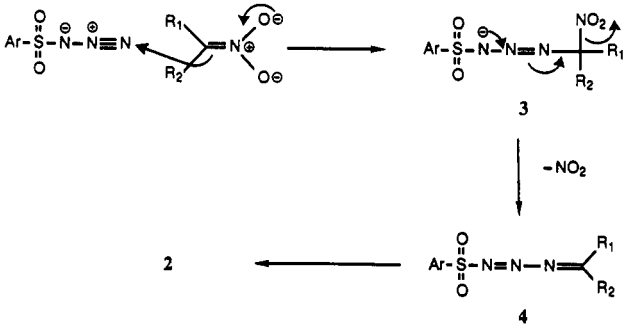
(2) Balli, H.; Low, R. *Tetrahedron Lett.* **1966**, 5821.
(3) Weininger, S. J.; Kohen, S.; Mataka, S.; Koga, N.; Anselme, J.-P. *J. Org. Chem.* **1974**, *39*, 1591.
(4) Smith, P. A. S.; Rowe, C. D.; Bruner, L. B. *J. Org. Chem.* **1969**, *34*, 3430.
(5) (a) Oxidation of azido sulfides: Böhme, H.; Morf, D. *Chem. Ber.* **1957**, *90*, 446. (b) $S_{RN}1$ reaction of α-nitro azides with sulfinates: Al-Khalil, S. I.; Bowman, W. R. *Tetrahedron Lett.* **1982**, 4513.

0022-3263/87/1952-3466$01.50/0

Table I

	2	yield, %
a	$R_1 = CH_3$, $R_2 = CH_2CH_2C(CH_3)O(CH_2)_2O$	35
b	$R_1,R_2 = (CH_2)_5$	56
c	$R_1,R_2 = CH_3$	49
d	$R_1 = CH_3$, $R_2 = H$	37
e	$R_1,R_2 = H$	0

Scheme I



primary, secondary, and cyclic nitroalkanes but fails with nitromethane (*p*-toluenesulfonamide was isolated as the only chromatographically mobile product in this case).[6] The β,γ-unsaturated substrate, 1-(nitromethyl)cyclohexene, gave a complex mixture of products that were unstable to SiO_2 chromatography. Although analytical evidence pointed to the azido sulfone structure for compounds **2**, the curious nature of this transformation (i.e., the net insertion of a carbon atom into a S–N bond with loss of nitrite) compelled us to confirm the identity of **2d** by unequivocal synthesis.[5a] Thus, treatment of ethyl *p*-tolyl sulfide with *N*-chlorosuccinimide in CCl_4 followed by NaN_3 in aqueous ethanol gave 1-azidoethyl *p*-tolyl sulfide (48%); subsequent oxidation with *m*-CPBA in CH_2Cl_2 furnished **2d** in 63% yield.

Mechanistically, we speculate that the first step in the conversion of the nitronate salts derived from **1** to azides **2** parallels that of normal diazo transfer[1] and the Dimroth reaction,[7] i.e., attack of the carbon nucleophile on the terminal azide nitrogen (Scheme I). 1,4-Elimination of nitrite from triazene **3** would then produce diene **4**. Analogous intermediates have been postulated in at least two variants of the Dimroth reaction,[8] and we have detected the production of nitrite during the formation of **2** by colorimetric analysis.[9] Finally, nitrogen to carbon migration of the aryl sulfone moiety is envisioned to lead to the observed products. That this latter process is one of dissociation–recombination is suggested by the results of a crossover experiment. When the potassium salt of nitrocyclohexane was treated with tosyl azide in the presence of 1 equiv of sodium *p*-bromobenzenesulfinate, a 2:1 mixture of **2b** and the corresponding *p*-bromo sulfone was produced. A control experiment showed that azide transfer from tosyl azide to the added sulfinate is very slow (ca. 2% in 48 h at 25 °C) under the reaction conditions employed. Furthermore, **2** was recovered unchanged after a 1-h exposure to sodium *p*-bromobenzenesulfinate in THF at 25 °C, indicating that exchange of the aryl sulfone group does not occur after the formation of **2**.

Experimental Section

General. Proton NMR spectra were recorded on a Varian XL-200 (200 MHz), T-60 (60 MHz), or IBM WP-100 (100 MHz) instruments, with $CHCl_3$ and/or Me_4Si as internal standards. All azido sulfones displayed the following resonances characteristic of the tosyl group: δ 7.8 (d, J = 8 Hz, 2 H), 7.3 ± 0.1 (d, J = 8 Hz, 2 H), 2.5 (s, 3 H). Infrared spectra were obtained on a Perkin-Elmer 298 spectrophotometer in the solvent indicated. Mass spectra were obtained with a Hewlett-Packard 5987A unit at 70 eV. Melting points were taken with a Thomas-Hoover apparatus and are uncorrected. Elemental analysis was performed by Robertson Laboratory, Madison, NJ. Reagents and solvents were reagent grade and used without purification except for tetrahydrofuran (THF), which was distilled from sodium/benzophenone immediately before use. Although combustion analysis within ±0.4% could not be obtained for **2c** and **2d**, NMR integration and MS data of freshly prepared samples suggested that these compounds were at least 90% pure.

General Procedure. Preparation of 2-Methyl-2-[3-(tolylsulfonyl)-3-azidobutyl]-1,3-dioxolane (2a). 2-Methyl-2-(3-nitrobutyl)-1,3-dioxolane[10] (0.7 g, 3.7 mmol) in 5 mL of dry THF was added to a suspension of KH (3.7 mmol; 0.42 g of 35% suspension in oil) in 5 mL of dry THF at room temperature under an atmosphere of nitrogen. The mixture was warmed to 40 °C and stirred until the evolution of hydrogen ceased (15 min). After the mixture was cooled to −10 °C, a solution of toluenesulfonyl azide (0.8 g, 4 mmol) in 5 mL of THF was added. The reaction mixture was allowed to warm to 0 °C, stirred for 1 h, and then partitioned between ether and 1 N NaOH. The organic phase was dried (Na_2SO_4), filtered, and evaporated. The residue was flash chromatographed (SiO_2; ethyl acetate/hexane, 1:5), giving 0.44 g (35%) of **2a**: mp 85–87 °C; IR (CCl_4) 2990, 2890, 2110 (s), 1315, 1230, 1150 (s), 1070 cm^{-1}; 200-MHz ^1H NMR ($CDCl_3$) δ 3.9 (m, 4 H), 2.1–1.65 (m, 4 H), 1.5 (s, 3 H), 1.26 (s, 3 H); MS (chemical ionization), m/e (relative intensity) 340 (0.1, M + 1), 156 (96), 115 (100).

Anal. Calcd for $C_{15}H_{21}N_3O_4S$: C, 53.08; H, 6.24; N, 12.39. Found: C, 52.80; H, 6.43; N, 12.38.

1-(Tolylsulfonyl)-1-azidocyclohexane (2b): mp 92–94 °C; IR (CCl_4) 2940, 2860, 2110 (s), 1310 (s), 1300, 1150, 1135 (s) cm^{-1}; 100-MHz ^1H NMR ($CDCl_3$) δ 2.1–1.1 (m, 10 H); MS, m/e (relative intensity) 155 (8), 96 (100), 91 (90), 55 (80).

Anal. Calcd for $C_{13}H_{17}N_3O_2S$: C, 55.89; H, 6.13; N, 15.04. Found: C, 55.81; H, 6.11; N, 15.01.

2-(Tolylsulfonyl)-2-azidopropane (2c): (oil); IR (CCl_4) 3050, 2950, 2120 (s), 1600, 1330 (s), 1250 (s), 1150 (s), 1130 (s), 1100 cm^{-1}; 60-MHz ^1H NMR ($CDCl_3$) δ 1.5 (s, 6 H); MS, m/e (relative intensity) 91 (20), 89 (10), 56 (100).

1-(Tolylsulfonyl)-1-azidoethane (2d): (oil); IR (CCl_4) 3050, 2950, 2110 (s), 1600, 1325 (s), 1170 cm^{-1}; 60-MHz ^1H NNR ($CDCl_3$) δ 4.2 (q, J = 7 Hz, 1 H), 1.5 (d, J = 7 Hz, 3 H); MS, m/e (relative intensity) 225 (0.1, M^+), 155 (6), 139 (12), 91 (100).

Alternate Preparation of 2d for Correlation. Ethyl *p*-tolyl sulfide (0.86 g, 5.7 mmol) and *N*-chlorosuccinimide (0.84 g, 6.3 mmol) were combined in 10 mL of CCl_4 and stirred at 25 °C for 5 h. The mixture was filtered, and the solvent was removed in vacuo. To this crude chloro sulfide was added a solution of sodium azide (1.1 g, 16.8 mmol) in 15 mL of ethanol and 10 mL of water. After the mixture was stirred for 1.5 h at 25 °C, most of the ethanol was removed in vacuo, and the residue was extracted into ether. After drying (Na_2SO_4), filtration, and evaporation, the residue was flash chromatographed (SiO_2; ethyl acetate/hexane, 2:98) to yield 0.531 g (48%) of *p*-tolyl 1-azidoethyl sulfide as a colorless oil: IR (CCl_4) 3030, 2980, 2920, 2110 (s), 1490, 1250, 1220, 1210 cm^{-1}; 60-MHz ^1H NMR ($CDCl_3$) δ 7.2 (d, J = 8 Hz, 2 H), 6.9 (d, J = 8 Hz, 2 H), 4.4 (q, J = 7 Hz, 1 H), 2.25 (s, 3 H), 1.4 (d, J = 7 Hz, 3 H). To the above azido sulfide (0.217 g, 1.12 mmol) in 4 mL of CH_2Cl_2 at 0 °C was added *m*-chloroperbenzoic acid (2.46 mmol; 0.53 g of 85% commercial *m*-CPBA) with stirring. The mixture was allowed to warm to 25 °C over 1 h and then worked

(6) This a byproduct in the reaction of certain aryl Grignard reagents with tosyl azide which also produces azo compounds: see, ref 4.

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up by extraction with 2 *M* aqueous sodium hydroxide solution. The organic phase was dried (Na_2SO_4), filtered, and evaporated. Flash chromatography of the residue (SiO_2; ethyl acetate/hexane, 1:9) afforded 0.156 g (63%) **2d**, identical in all respects (TLC, IR, NMR, and MS) with a sample obtained from the reaction of potassium ethyl nitronate with *p*-toluenesulfonyl azide.

Crossover Experiment. Preparation of 2b with Added *p*-Bromobenzenesulfinate. A suspension of the potassium salt of nitrocyclohexane (3.5 mmol) was prepared in 15 mL of THF as described above. Sodium *p*-bromobenzenesulfinate (3.5 mmol, 0.85 g) and tosyl azide (3.5 mmol, 0.69 g) were added, and the mixture was stirred for 20 h. The reaction mixture was partitioned between ether and 2 N NaOH. The organic phase was dried (Na_2SO_4), filtered, and evaporated. At this point, the reaction mixture was indistinguishable by TLC from the reaction which yielded **2b** alone. The product (0.49 g) was isolated by flash chromatography (SiO_2, ethyl/hexane, 1:20) and examined by ^1H NMR (200 MHz, $CDCl_3$). Integration of the doublet at δ 7.35 and the multiplet at δ 7.7 indicated that 33% of the *p*-bromobenzenesulfinate had been incorporated. As a control, tosyl azide (2 mmol, 0.42 g) and sodium *p*-bromo benzenesulfinate (2 mmol, 0.62 g) were stirred in THF at 25 °C for 46 h. Workup and chromatography as above gave 0.4 g (97%) of recovered tosyl azide and 0.01 g (2.4%) of *p*-bromobenzenesulfonyl azide.

Acknowledgment. This work was supported by a grant from the Research Corporation.

Registry No. **1a**, 84602-25-5; **1b**, 1122-60-7; **1c**, 79-46-9; **1d**, 79-24-3; **2a**, 108795-74-0; **2b**, 108795-75-1; **2c**, 108795-76-2; **2d**, 108795-77-3; 4-$H_3CCH_2SC_6H_4CH_3$, 622-63-9; 4-$H_3CCHClSC_6H_4CH_3$, 59480-99-8; 4-$H_3CC_6H_4SO_2N_3$, 941-55-9; 4-$BrC_6H_4SO_3Na$, 34176-08-4; 4-$H_3CC_6H_4SCHN_3CH_3$, 108795-78-4; 4-$BrC_6H_4SO_2N_3$, 6647-76-3.

Synthesis of HT-2 Toxin, Neosolaniol, T-2 Toxin, 3′-Hydroxy T-2 Toxin, and Sporotrichiol from Anguidine by Routes Involving Hydroxyl Inversion/Esterification

Mansukh C. Wani,* Douglas H. Rector, and C. Edgar Cook*

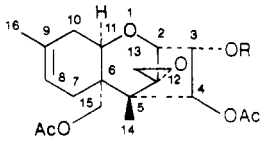
Chemistry and Life Sciences, Research Triangle Institute, Research Triangle Park, North Carolina 27709

Received February 12, 1987

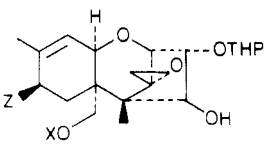
Trichothecenes are a group of more than 50 sesquiterpenoid mycotoxins produced by many fungi.[1] These mycotoxins have been responsible for human and animal toxicoses resulting from consumption of contaminated foodstuff.[1,2] Furthermore, in the recent past, there has been considerable interest in T-2 toxin (**11**) and related mycotoxins because of controversy over their alleged use in chemical/biological warfare in Afghanistan and Southeast Asia.[3]

In connection with our work on the preparation of antisera for the detection of trichothecene mycotoxins in the environment, we needed a hapten with a hemisuccinate ester at C-4 for coupling to the carrier protein. The synthesis of the 4α,8β-dihydroxy precursor **5** (Chart I) of the desired hapten was readily accomplished by selenium dioxide oxidation of the known compound **4**.[4] To convert

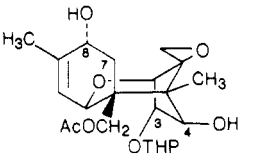
Chart I



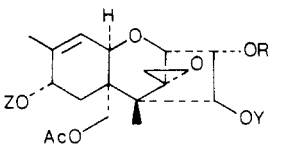
1, R=H
2, R=THP



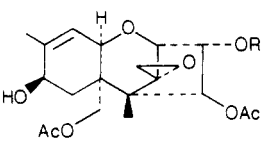
3, X=H, Z=H
4, X=Ac, Z=H



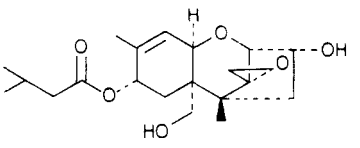
5



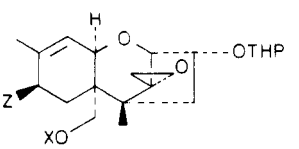
8, R=THP, Y=H, Z=
9, R=H, Y=H, Z=
10, R=H, Y=Ac, Z=H
11, R=H, Y=Ac, Z=
12, R=H, Y=Ac, Z=



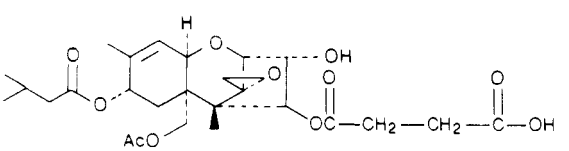
6, R=H
7, R=THP



17



13, X=Ac, Z=H
14, X=H, Z=H
15, X=formyl, Z=H
16, X=formyl, Z=OH



18

5 to the 8α-isovaleryloxy compound **8**, we examined a procedure used for the inversion of steroid alcohols to their formate esters of the opposite configuration.[5] Compound **5** reacted smoothly with diethyl azodicarboxylate (DEAD), triphenylphosphine, and isovaleric acid to yield **8**. This was succinylated and the THP ether cleaved to yield the desired hapten **18**.[6] The ease of inversion of configuration at C-8 led us to examine its applicability to the synthesis of other trichothecenes. In this paper, we report the synthesis of several naturally occurring mycotoxins including the recently isolated sporotrichiol[7] (**17**, 8α-[(3-methylbutyryl)oxy]scirpene-3α,15-diol) from the readily available trichothecene anguidine (**1**, 4β,15-diacetoxyscirpen-3β-ol) using the above methodology. The synthesis of **17** confirms the assigned structure of this natural product.

The synthesis of all the five trichothecenes, HT-2 toxin (**9**, 15-acetoxy-8α-[(3-methylbutyryl)oxy]scirpene-3α,4β-

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