DBU-Mediated cleavage of aryl- and heteroaryl disulfides

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Abstract

The capacity of the nitrogen nucleophile, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to reduce aryl- and heteroaryl disulfides to the corresponding mercaptans is demonstrated. While dicarboxylated disulfide analogues afford the mono-DBU disulfide salts, as confirmed by X-ray crystallography, the corresponding methyl esters are cleaved normally.

Keywords: Disulfide cleavage, aryl disulfides, DBU, aryl mercaptans

Introduction

The synthesis of 2H-1-benzo thiopyrans (thiochromenes) has typically involved the condensation of thiophenols with acrylic acid derivatives, followed by reduction and dehydration, and a number of approaches to these systems have been reported. As part of our ongoing research on applications of Baylis-Hillman methodology, we reported the convenient, one-step synthesis of the thiochromenes 3a-g via the 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)-catalyzed reaction of 2,2'-dithiodibenzaldehyde 1a with activated alkenes 2a-g (Scheme 1). The thiochromenes 3a-g were obtained in a single step – an observation that suggested the capacity of DBU to reduce the disulfides 4a-g (formed via the Baylis Hillman reaction), possibly via the sequence outlined in Scheme 1. Phosphine nucleophiles have been implicated in the direct cleavage of disulfides, while photo-induced cleavage via disulfide radical anions has been attributed to electron transfer from excited-state aniline and various amines have been used in large excess (40 eq.) to produce, in situ at elevated temperatures, benzenethiyl radicals from diphenyl disulfide via a single electron transfer process. DBU has been used as a base in thiazolium salt-catalyzed disulfide reduction–aldehyde oxidation processes but, to our knowledge, its role as a nucleophile in the direct cleavage of disulfides is unprecedented. We now report the results of further research directed at exploring the general capacity of DBU to reduce diaryl and
het erodiaryl disulfides to mercaptans in the absence of an activated alkene, thus precluding involvement of a Baylis-Hillman adduct, as suggested in Scheme 1.

Scheme 1. Synthetic pathway and putative mechanism to account for the formation of the thiochromenes 3a-g.

Results and Discussion

In order to investigate the potential of DBU to serve as a disulfide reducing agent, solutions of the nine disulfides 1a-i (Scheme 2) in chloroform were treated with DBU in the same molar ratios and under the same reaction conditions used in the previously reported Baylis-Hillman reactions, but without any activated alkene. [Under these conditions, accommodation of the nucleofugal sulfide by a pre-formed Baylis-Hillman adduct (as suggested in Scheme 1) would be precluded.] In most cases, the expected mercaptans (9a-f) were, in fact, isolated in low to moderate yield (13 - 53%), demonstrating the ability of DBU to effect reductive cleavage of the disulfide bonds in these compounds. The carboxylic acid derivatives 1g-i, however, afforded crystalline products, NMR analysis of which initially suggested possible trapping of the putative oxidised DBU cation 8 (Scheme 1). Single-crystal X-ray analysis (Figure 1) of the product obtained using the dicarboxylic acid 1i, however, confirmed the formation of the corresponding
mono-DBU-disulfide salt 10i.\(^{11}\) Formation of the salts 10g-i prompted synthesis of the corresponding methyl esters 1d-f.

When the substrate 1a was dissolved in CDCl\(_3\) alone, no change was observed after 14 days, confirming that DBU is, in fact, responsible for the observed disulfide cleavage. When the disulfide 1a was treated with DBU in the dark, normal disulfide cleavage was observed thus excluding a photo-induced, free-radical process.

**Scheme 2.** Reaction of disulfides 1a-i with DBU in chloroform.
Figure 1. X-Ray crystal structure of the mono-DBU salt 10i of dicarboxylic acid 1i showing the crystallographic numbering for the asymmetric unit and thermal ellipsoids drawn at the 50% probability level.

Conclusions

DBU is clearly capable of direct reductive cleavage of the diaryl and heterodiaryl disulfides 1a-f. Optimization and extension of the methodology to aliphatic disulfides may provide an effective alternative, in certain applications, to the use of more established reagent systems. The thiophilicity of DBU 7 in these reactions may be attributable to the intramolecular delocalisation effects illustrated in structure 7 in Scheme 1.

Experimental Section

General. Reagents, as supplied by Aldrich-Sigma, and solvents were used without further purification. $^1$H and $^{13}$C NMR spectra were recorded on Bruker AMX400 or Avance II+ 600 MHz spectrometers, and were calibrated using solvent signals; coupling constants are given in Hertz (Hz). Melting points were determined using a hot-stage apparatus, and are uncorrected. IR spectra were recorded on a Perkin Elmer Spectrum 100 FT-IR spectrometer. High-resolution mass spectra were recorded by the University of Stellenbosch Mass Spectrometry Unit. Flash chromatography was carried out using Merck silica gel 60 [230-240 mesh (particle size 0.040-
0.063 mm) and preparative layer chromatography was conducted using silica gel 60 PF254. HPLC was carried out on a Partisil 10 Magnum 6 normal phase column using a Spectra-Physics P100 isocratic pump and a Waters K1410 differential refractometry detector.

General procedures and analytical data for new compounds are as follows.

Reactions of DBU with disulfides (1a-f)

General procedure, exemplified by the preparation of 2-mercaptobenzaldehyde (9a)

DBU (0.11 mL, 0.75 mmol) was added slowly to a stirred solution of 2,2'-dithiodibenzaldehyde (0.1 g) in CHCl₃ (0.7 mL). The mixture was further stirred in a stoppered flask for 2 weeks. Flash chromatography [elution with hexane–EtOAc (1:1)] gave the known compound.¹² 2-mercaptobenzaldehyde 9a (0.15 g, 49%) as a yellow oil, HPLC of which afforded analytical material (Found M-H: 137.0055. C₇H₅OS requires: 137.0061; v_max/cm⁻¹ (neat) 2612 (S-H) and 1686 (C=O); δ_H (400 MHz; CDCl₃) 5.96 (1H, d, J = 3.49 Hz, SH), 7.41 (1H, t, J = 7.45 Hz, 5-H), 7.58 (1H, dd, J = 7.48 and 1.37 Hz, 6-H), 7.85 (1H, t, J = 8.08 Hz, 4-H), 7.93 (1H, d, J = 7.97 Hz, 3-H) and 10.14 (1H, s, CHO); δ_C (100 MHz; CDCl₃) 127.4 (C-5), 128.2 (C-4), 129.3 (C-6), 130.4 (C-3), 134.1 (C-1), 134.8 (C-2) and 192.1 (CHO); m/z 137 (M⁺, 100%).

Other known compounds to be isolated were:

2-Mercapto-1,3-benzothiazole (9b) as a yellow crystalline solid (0.08 g, 53%), m.p. 154-156 °C (Lit.¹³ 177-179 °C) (Found M⁺: 65.9779. C₇H₆NS₂ requires: 165.9785); v_max/cm⁻¹ (neat) 2572 (S-H) and 1464 (C=N); δ_H (400 MHz; CDCl₃) 3.52 (1H, s, SH), 7.28 (1H, m, 5-H), 7.37-7.39 (2H, m, 4H and 7-H), 7.46 (1H, m, 6-H); δ_C (150 MHz; CDCl₃) 112.4 (C-5), 121.8 (C-6), 125.1 (C-4), 127.6 (C-7), 130.5 (C-3a), 140.5 (C-7a), 191.2 (C-2); m/z 166 (M⁺, 100%).

Methyl 2-mercaptobenzonate (9d)¹⁴ as a yellow oil (0.03 g, 20%) (Found M⁺: 167.0167. C₇H₇O₂S requires: 167.0171); v_max/cm⁻¹ (neat) 2556 (S-H) and 1704 (C=O); δ_H (400 MHz; CDCl₃) 3.84 (1H, s, SH), 3.97 (3H, s, OCH₃), 7.19-7.22 (1H, m, Ar-H), 7.40 (1H, t, J =7.73 Hz, Ar-H), 7.74 (1H, d, J = 8.17 Hz, Ar-H) and 8.05 (1H, d, J = 7.01 Hz, Ar-H); δ_C (100 MHz; CDCl₃) 52.4 (OCH₃), 125.5, 125.9, 127.3, 131.5, 133.1 and 140.4 (Ar-C) and 166.9 (C=O); m/z 167 (M⁺, 100%).

Analytical data for new compounds are as follows

2-Mercapto-4-Nitropyridine (9c) as a brown solid (0.0582 g, 30%), m.p. 96-98 °C (Found M⁺: 154.9900. C₅H₄N₂O₂S requires: 154.9915); v_max/cm⁻¹ (neat) 2511 (S-H) and 1565 (C=N); δ_H (400 MHz; CDCl₃) 6.81 (1H, d, J = 9.63 Hz, 6-H), 8.33 (1H, dd, J = 9.53 and 1.99 Hz, 5-H) and 9.07 (1H, s, 2-H); δ_C (100 MHz; CDCl₃) 119.8, 132.1, 142.7, 145.3 and 165.0 (Ar-C); m/z 155 (M⁺, 100%).

Methyl 2-mercapto-6-nitrobenzoate (9e) as a yellow oil (0.017 g, 44%) (Found M⁺: 212.0018. C₈H₈NO₄S requires: 212.0022); v_max/cm⁻¹ (neat) 2612 (S-H) and 1732 (C=O); δ_H (400 MHz; CDCl₃) 3.72 (3H, s, OCH₃), 5.42 (1H, m, SH), 7.60 (2H, m, Ar-H), 7.82 (1H, m, Ar-H) and 8.19...
(1H, m, Ar-H); δ_C (100 MHz; CDCl_3) 53.3 (OCH_3), 111.1, 124.9, 126.2, 128.3, 133.9 and 146.2 (Ar-C) and 171.1 (C=O); m/z 212 (M^+, 52%) and 259 (100%).

**Methyl 6-mercaptopyridine-3-carboxylate (9f)** as a yellow oil (0.02 g, 13%) (Found M^+: 170.0276. C_7H_8NO_2S requires: 170.0273); v_max/cm^{-1} (neat) 3054 (S-H) and 1714 (C=O); δ_H (400 MHz; CDCl_3) 3.92 (1H, s, SH), 3.95 (1H, s, OCH_3), 7.61 (1H, d, J = 8.32 Hz, Ar-H), 8.21 (1H, d, J = 8.31 and 2.24 Hz, Ar-H), 9.10 (1H, s, 2-H); δ_C (100 MHz; CDCl_3) 52.9 (OCH_3), 125.4, 138.20, 138.23, 151.58 and 151.60 (Ar-C) and 165.7 (C=O); m/z 170 (M^+, 30%) and 182 (100%).

**Esterification of disulfide dicarboxylic acids (1g-i)**

General procedure, exemplified by the preparation of methyl 2-(methoxycarbonylphenyl)disulfanylbenzoate (1d)

H_2SO_4 (0.4 mL) was added to MeOH (30 mL), followed by 2,2'-dithiodibenzoic acid 1g (6 g, 0.02 mol), and the resulting mixture was refluxed for 5 h. After cooling, H_2O (30 mL) was added and the mixture was stirred for several minutes, before adding further H_2O (30 mL) followed by satd. q. NaHCO_3 (15 mL). The precipitated solid was filtered off and washed with a little H_2O to give methyl 2-(methoxycarbonylphenyl)disulfanylbenzoate 1d as a cream powder (13.3 g, 49%), m.p. 172-173 °C [Found (M - C_2H_7)^+: 303.0676. C_{16}H_{13}NOS_2 requires: 302.97857]; v_max/cm^{-1} (neat) 1661 (C=O); δ_H (400 MHz; CDCl_3) 3.98 (6H, s, OCH_3), 7.23 (2H, t, J = 5.77 Hz, Ar-H), 7.40 (2H, m, Ar-H), 7.52 (2H, d, J = 8.07 Hz, Ar-H) and 8.05 (2H, dd, J = 7.78 and 1.22 Hz, Ar-H); δ_C (100 MHz; CDCl_3) 52.3 (OCH_3), 125.5, 125.9, 127.3, 131.5, 133.1 and 140.4 (Ar-C) and 166.9 (C=O); m/z 303 [(M - C_2H_7)^+, 30%] and 325 (100%).

**Methyl 2-(2-methoxycarbonyl-3-nitrophenyl)disulfanyl-6-nitrobenzoate (1e)** as a yellow oil (0.03 g, 57%) (Found MH^+: 425.0009. C_{18}H_{13}N_2O_3S_2 requires: 425.01077); v_max/cm^{-1} (neat) 1724 (C=O); δ_H (400 MHz; CDCl_3) 3.92 (6H, s, OCH_3), 7.87 – 7.94 (6H, series of multiplets, Ar-H); δ_C (100 MHz; CDCl_3) 53.6 (OCH_3), 125.1, 126.8, 127.2, 128.4, 129.0, 142.5 (Ar-C) and 167.7 (C=O).

**Methyl 6-[(5-methoxycarbonyl-2-pyridyl)disulfanyl]pyridine-3-carboxylate (1f)** as a cream solid (1.7 g, 70%), m.p. 149-151 °C [Found (M - C_2H_7)^+: 305.0597. C_{12}H_{13}N_2O_2S requires: 304.9692]; v_max/cm^{-1} (neat) 1716 (C=O); δ_H (400 MHz; CDCl_3) 3.92 (6H, s, OCH_3), 7.64 (2H, d, J = 8.41 Hz, Ar-H), 8.18 (2H, d, J = 8.38 Hz, Ar-H) and 9.04 (2H, s, Ar-H); δ_C (100 MHz; CDCl_3) 52.6 (OCH_3), 124.1, 125.4, 138.1, 150.5, 164.8 (Ar-C) and 165.8 (C=O); m/z 305 [(M - C_2H_7)^+, 100%]

. Formation of mono-DBU disulfide dicarboxylic acid salts (10g-i)

The mono-DBU salt (10i). The general procedure described for the synthesis of 2-mercaptobenzaldehyde (9a) was followed using 5,5'-dithiobis-(2-nitrobenzoic) acid (0.1 g, 0.9 mmol), DBU (0.1 mL, 2 mmol) and CHCl_3 (1.0 mL). Work up afforded a yellow solid which was recrystallised from EtOH to give the mono-DBU salt 10i (0.12 g, 68%) as yellow crystals, m.p. 217-220 °C; v_max/cm^{-1} (neat) 1689 (C=O) and 1560 (C=N); δ_H (600 MHz; CDCl_3) 1.63-1.71
(6H, m, DBU-CH₂), 1.89 (2H, m, DBU-CH₂), 2.65 (2H, m, DBU-CH₂), 3.22 (2H, br s, DBU-CH₂), ca. 3.5 (4H, overlapping H₂O signal, DBU-CH₂), 7.48 (1H, dd, J = 8.46 and 2.20 Hz, Ar-H), 7.69 (H, m, Ar-H), 7.73 (1H, s, Ar-H) and 10.15 (1H, s, CO₂H); δC (150 MHz; CDCl₃) 18.9, 23.4, 25.9, 28.2, 31.5, 37.5, 47.8, 53.3 (DBU-C), 99.5 (C=N), 124.0, 125.5, 126.2, 139.7, 147.0 and 165.3 (Ar-C) and 168.8 (C=O).

The mono-DBU salt (10g). (0.39g, 70%) as a cream solid, m.p. 213-216 °C; v₁max/cm⁻¹ (neat) 1672 (C=O) and 1572 (C=N); δH (600 MHz; CDCl₃) 1.59-1.66 (6H, m, DBU-CH₂), 1.88-1.91 (2H, m, DBU-CH₂), 2.75 (2H, m, DBU-CH₂), 3.45-3.55 (6H, overlapping H₂O signal, DBU-CH₂), 7.06 (1H, t, J = 7.23 Hz, Ar-H), 7.13 (1H, t, J = 7.51 Hz, Ar-H), 7.45 (1H, d, J = 8.00 Hz, Ar-H), 7.80 (1H, d, J = 7.43 Hz, Ar-H) and 8.27 (1H s, CO₂H); δC (150 MHz; CDCl₃) 18.9, 23.3, 25.9, 28.1, 31.3, 37.5, 47.7, 53.2 (DBU-C), 97.6 (C=N), 123.6, 123.7, 128.3, 129.9, 132.8 and 165.3 (Ar-C) and 168.3 (CO₂H).

The mono-DBU salt (10h) (0.33g, 59%) as a brown solid, m.p. 207-209 °C; v₁max/cm⁻¹ (neat) 1662 (C=O) and 1606 (C=N); δH (400 MHz; CDCl₃) 1.64-1.72 (6H, m, DBU-CH₂), 1.98 (2H, m, DBU-CH₂), 2.86 (2H, m, DBU-CH₂), ca. 3.5 (6H, overlapping H₂O signal, DBU-CH₂), 7.55 (1H, d, J = 8.31 Hz, Ar-H), 8.20 (1H, dd, J = 8.32 and 2.03 Hz, Ar-H), 8.84 (1H, s, Ar-H) and 9.04 (1H, s, CO₂H); δC (150 MHz; CDCl₃) 18.9, 23.4, 26.0, 28.3, 31.5, 37.6, 47.8, 53.3 (DBU-C), 108.6 (C=N), 118.4, 138.4, 150.5, 158.2 and 165.3 (Ar-C) and 166.3 (C=O).

Crystal data for the mono{1,8-diazabicyclo[5.4.0]undec-7-ene} salt of 5,5'-dithiobis(2-nitrobenzoic acid)(10i). (C₁₄H₇N₂O₈S₂)⁺ (C₉H₇N₂)⁺, M = 548.58, 0.18 x 0.16 x 0.13 mm³, triclinic, space group P(-1) (No. 2), a = 10.1019(8), b = 10.4227(8), c = 12.3805(9) Å, α = 77.899(2), β = 74.919(2), γ = 80.698(2)°, V = 1222.73(16) Å³, Z = 2, Dc = 1.490 g/cm³, F₀₀₀ = 572, MoKα radiation, λ = 0.71073 Å, T = 173(2)K, 2θmax = 56.7°, 48890 reflections collected, 6080 unique (Rint = 0.0435). Final GooF = 1.049, R₁ = 0.0361, wR₂ = 0.0912, R indices based on 5006 reflections with I >2σ(I) (refinement on F²), 353 parameters, 2 restraints. Lp and absorption corrections applied, μ = 0.275 mm⁻¹. Primary dihedral angles in the disulfide ion include C₁-S₁₃-S₁₄-C₁₅ -90.40(7)°, S₁₃-S₁₄-C₁₅-C₂₀ 15.1(1)° and S₁₄-S₁₃-C₁-C₆ 21.0(1)°. One of the methylene groups (C₂₉) is statistically disordered over two positions (a, b). Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-816182. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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References and Notes

11. The cation and anion are linked by the H-bond N27·H···O22 with N···O 2.823(2) Å; the anions are linked in infinite chains via a strong head-to-tail H-bond O8·H···O22' with O···O 2.473(2) Å (i = x,-1+y,1+z). The molecular symmetry indicated by the NMR spectra in some cases is attributed to dynamic proton transfer in solution.