DBU-Mediated cleavage of aryl- and heteroaryl disulfides

Dubekile Nyoni,[a] Kevin A. Lobb, [a] Perry T. Kaye [a]*and Mino R. Caira[b]

[a]Department of Chemistry, Rhodes University, Grahamstown, South Africa
[b]Department of Chemistry, University of Cape Town, Rondebosch, South Africa
E-mail: P.Kaye@ru.ac.za

DOI: http://dx.doi.org/10.3998/ark.5550190.0013.623

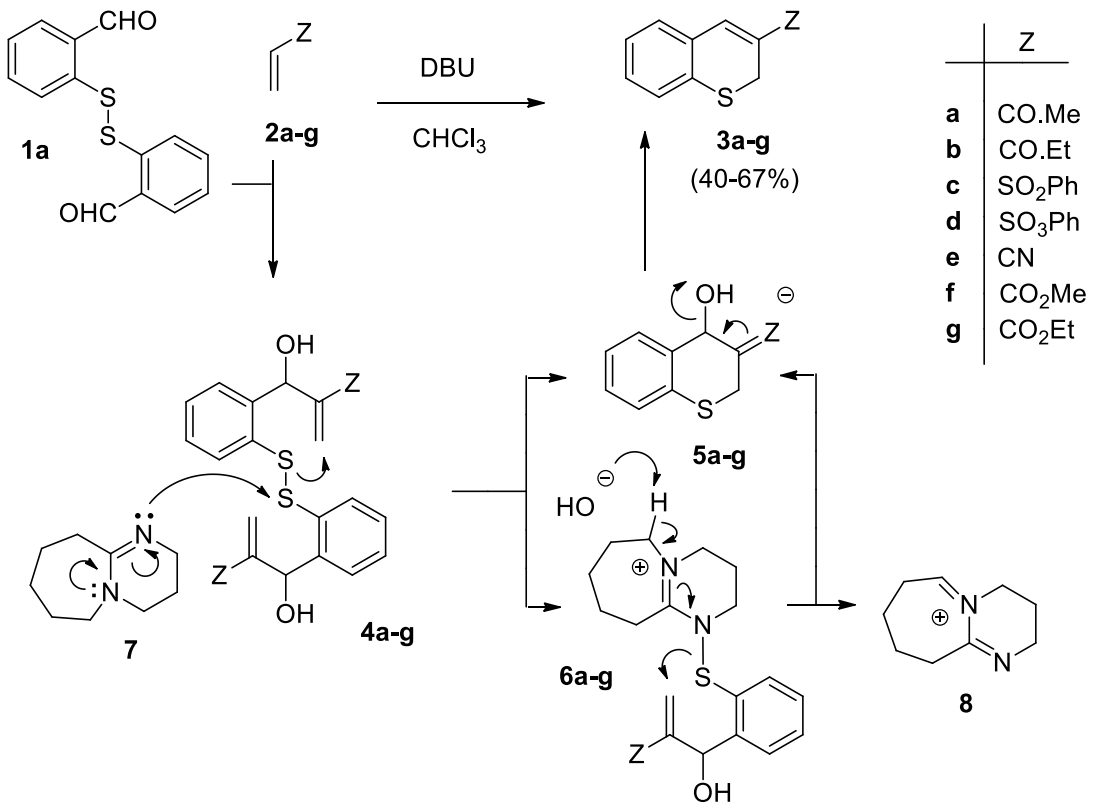
Abstract
The capacity of the nitrogen nucleophile, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to reduce aryl- and heteroaryl disulfides to the corresponding mercaptans is demonstrated. While dicarboxylated disulfide analogues afford the mono-DBU disulfide salts, as confirmed by X-ray crystallography, the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

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

Introduction

The synthesis of 2*H*-1-benzothiopyrans (thiochromenes) has typically involved the condensation of thiophenols with acrylic acid derivatives, followed by reduction and dehydration,[1] and a number of approaches to these systems have been reported.[2-4] As part of our ongoing research on applications of Baylis-Hillman methodology,[5] 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).[6] The thiochromenes **3a-g** were obtained in a single step − an observation that suggested the capacity of DBU to reduce the disufides **4a-g** (formed *via* the Baylis Hillman reaction), possibly *via* the sequence outlined in Scheme 1.[6] Phosphine nucleophiles have been implicated in the direct cleavage of disulfides,[7] while photo-induced cleavage *via* disulfide radical anions has been attributed to electron transfer from excited-state aniline[8] 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.[9] DBU has been used as a *base* in thiazolium salt-catalyzed disufide reduction–aldehyde oxidation processes[10] 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

heterodiaryl disulfides to mercaptans in the absence of an activated alkene, thus precluding involvement of a Baylis-Hillman adduct, as suggested in Scheme 1.



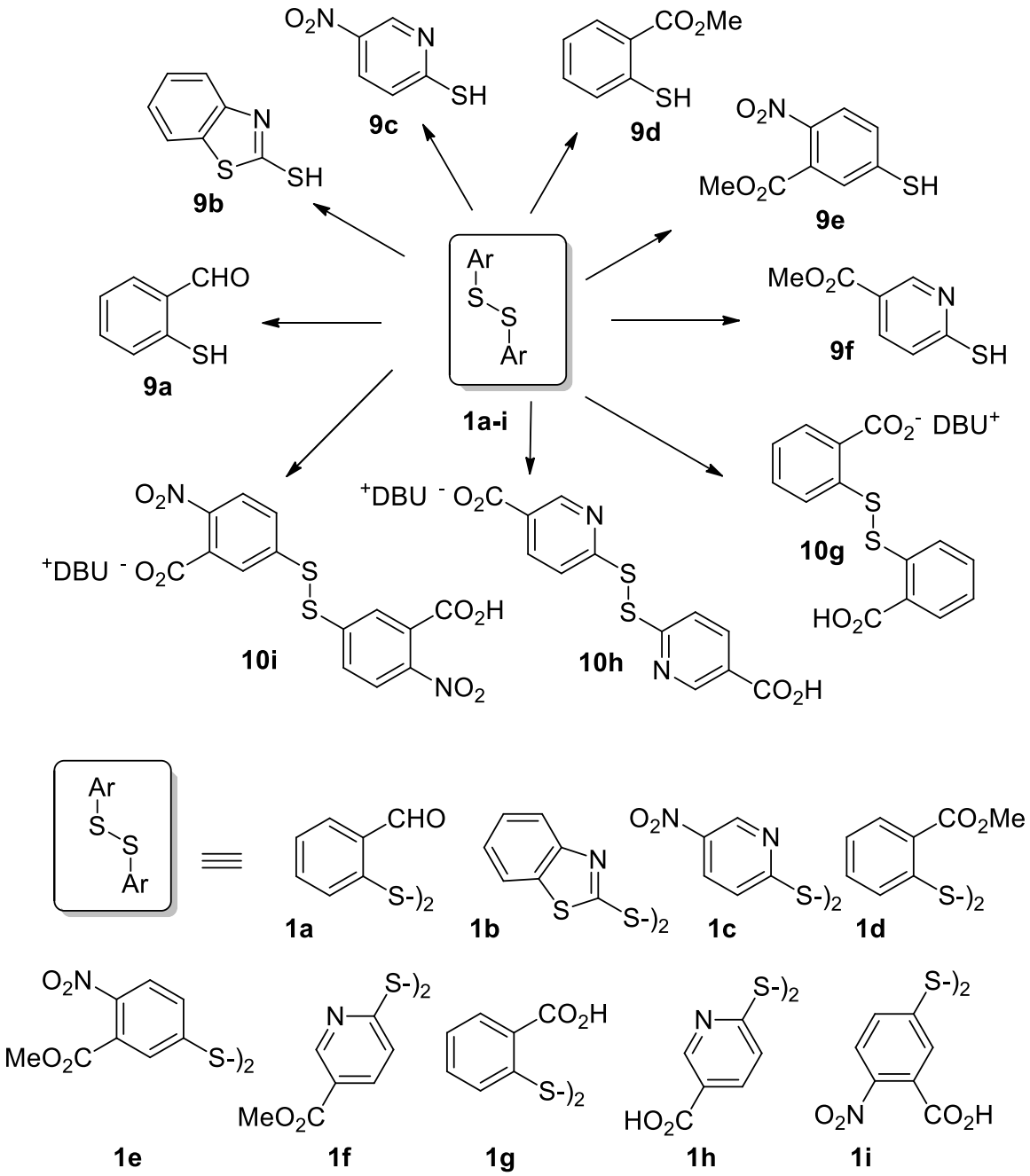
Scheme 1. Synthetic pathway and putative mechanism to account for the formation of the thiochromenes **3a-g**.[6]

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,[6] 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 disufide **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.

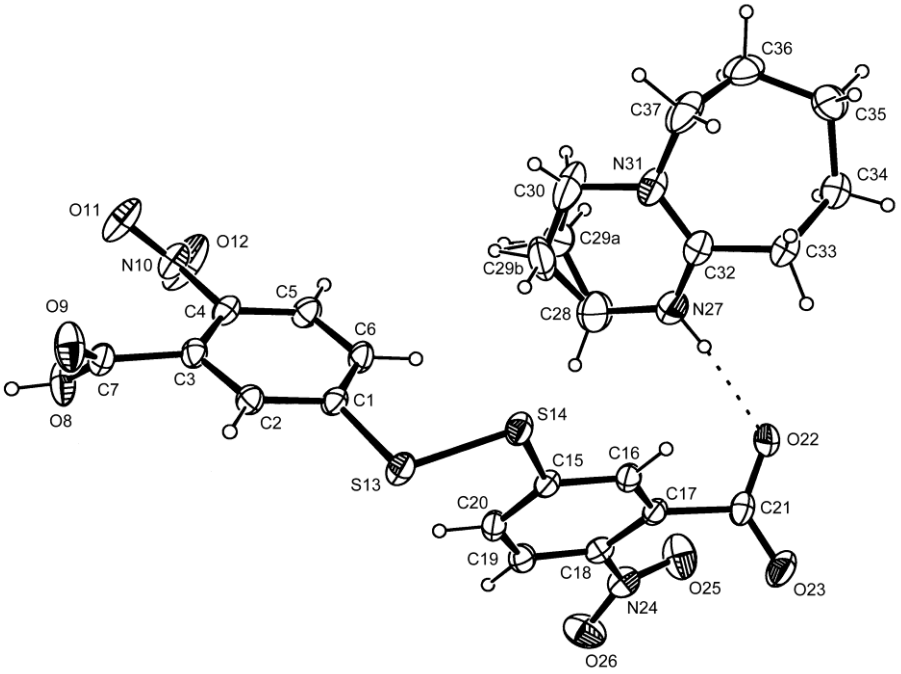


Figure 1. X-Ray crystal structure of the mono-DBU salt **10i** of dicarboxylic acid **1i** showing the crystallographic numbering for the asymmetric unit and thermal ellipsoids drawn at the 50% probability level.

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 PF_{254}. 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 $CHCl_3$ (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. C_7H_5OS requires: 137.0061); ν_{max}/cm^{-1} (neat) 2612 (S-H) and 1686 (C=O); δ_H (400 MHz; $CDCl_3$) 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; $CDCl_3$) 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. $C_7H_4NS_2$ requires: 165.9785);); ν_{max}/cm^{-1} (neat) 2572 (S-H) and 1464 (C=N); δ_H (400 MHz; $CDCl_3$) 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; $CDCl_3$) 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-mercaptobenzoate (9d)[14] as a yellow oil (0.03 g, 20%) (Found M^+: 167.0167. $C_8H_7O_2S$ requires: 167.0171); ν_{max}/cm^{-1} (neat) 2556 (S-H) and 1704 (C=O); δ_H (400 MHz; $CDCl_3$) 3.84 (1H, s, SH), 3.97 (3H, s, OCH_3), 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; $CDCl_3$) 52.4 (OCH_3), 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. $C_5H_3N_2O_2S$ requires: 154.9915); ν_{max}/cm^{-1} (neat) 2511 (S-H) and 1565 (C=N); δ_H (400 MHz; $CDCl_3$) 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; $CDCl_3$) 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. $C_8H_6NO_4S$ requires: 212.0022);); ν_{max}/cm^{-1} (neat) 2612 (S-H) and 1732 (C=O); δ_H (400 MHz; $CDCl_3$) 3.72 (3H, s, OCH_3), 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);); ν_{max}/cm^{-1} (neat) 2541 (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, dd, *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-(methoxycarbonyl-phenyl)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 5h. 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. aq. $NaHCO_3$ (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. $C_{14}H_7O_4S_2$ requires: 302.97857]; ν_{max}/cm^{-1} (neat) 1661 (C=O); δ_H (400 MHz; $CDCl_3$) 3.98 (6H, s, OCH_3), 7.23 (2H, t, *J* = 7.57 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. $C_{16}H_{13}N_2O_8S_2$ requires: 425.01077); ν_{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. $C_{12}H_5N_2O_4S_2$ requires: 304.9692]; ν_{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** (0.12g, 68%) as yellow crystals, m.p. 217-220 °C; ν_{max}/cm^{-1} (neat) 1689 (C=O) and 1560 (C=N); δ_H (600 MHz; $CDCl_3$) 1.63-1.71

(6H, m, DBU-CH_2), 1.89 (2H, m, DBU-CH_2), 2.65 (2H, m, DBU-CH_2), 3.22 (2H, br s, DBU-CH_2), *ca.* 3.5 (4H, overlapping H_2O signal, DBU-CH_2), 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, CO_2H); δ_C (150 MHz; $CDCl_3$) 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 ºC; ν_{max}/cm^{-1} (neat) 1672 (C=O) and 1572 (C=N); δ_H (600 MHz; $CDCl_3$) 1.59-1.66 (6H, m, DBU-CH_2), 1.88-1.91 (2H, m, DBU-CH_2), 2.75 (2H, m, DBU-CH_2), 3.45-3.55 (6H, overlapping H_2O signal, DBU-CH_2), 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, CO_2H); δ_C (150 MHz; $CDCl_3$) 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 (CO_2H).

The mono-DBU salt (10h) (0.33g, 59%) as a brown solid, m.p. 207-209 ºC; ν_{max}/cm^{-1} (neat) 1662 (C=O) and 1606 (C=N); δ_H (400 MHz; $CDCl_3$) 1.64-1.72 (6H, m, DBU-CH_2), 1.98 (2H, m, DBU-CH_2), 2.86 (2H, m, DBU-CH_2), *ca.* 3.5 (6H, overlapping H_2O signal, DBU-CH_2), 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, CO_2H); δ_C (150 MHz; $CDCl_3$) 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-diazabicylo[5.4.0]undec-7-ene} salt of 5,5'-dithiobis-(2-nitrobenzoic acid)(10i). $(C_{14}H_7N_2O_8S_2)^-$ $(C_9H_{17}N_2)^+$, M = 548.58, 0.18 x 0.16 x 0.13 mm^3, 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) $Å^3$, Z = 2, D_c = 1.490 g/cm^3, F_{000} = 572, MoKα radiation, λ = 0.71073 Å, T = 173(2)K, $2\theta_{max}$ = 56.7º, 48890 reflections collected, 6080 unique (R_{int} = 0.0435). Final $GooF$ = 1.049, R_1 = 0.0361, wR_2 = 0.0912, R indices based on 5006 reflections with $I > 2\sigma(I)$ (refinement on F^2), 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).

Acknowledgements

The authors thank the National Research Foundation (NRF: GUN 2069255) and Rhodes University for a bursary (D.N), Rhodes University, the University of Cape Town and the NRF for generous financial support. Any opinion, findings and conclusions or recommendations

expressed in this material are those of the authors and therefore the NRF does not accept any liability in regard thereto.

References and Notes

1. Ingall, A. H. In *Comprehensive Heterocyclic Chemistry*, Boulton, A. J.; McKillop, A. Eds., Vol. 3, Pergamon Press: Oxford, 1984, p 934.
2. Tercio, J.; Ferreira, B.; Catani, V.; Comasseto, J. V. *Synthesis* **1987**, 149-153.
3. Arnoldi, A.; Carughi, M. *Synthesis* **1988**, 155-157.
4. Kobayashi, K.; Konishi, H.; Kitamura, T.; Morikawa, O.; Nakahashi, R. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1547-1552.
5. (a) Bode, M. L.; Kaye, P. T. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2612-2613. (b) Bode, M. L.; Kaye, P.T.*J. Chem. Soc., Perkin Trans. 1* **1993**, 1809-1811. (c) Familoni, O. B.; Kaye, P. T.; Klaas, P. J. *Chem. Commun*. **1998**, 2563-2564. (d) Kaye, P. T.; Nocanda, X. W. *J. Chem. Soc., Perkin Trans. 1* **2000,** 1331-1332.
6. Kaye, P. T.; Nocanda, X. W. *Synthesis* **2001**, 2389-2392.
7. (a) Humphrey, R. E.; Hawkins, J. M. *Anal. Chem.*, **1964**, *36* (9), 1812–1814. (b) Dmitrenko, O.; Thorpe, C.; Bach, R. D. *J. Org. Chem.* **2007**, *77*(22), 8298-8307.
8. Changyuan, L.; Bucher, G.; Sander, W. *ChemPhysChem*. **2004**, *5*, 399-402.
9. Taniguchi, T.; Fujii, T.; Idota, A.; Ishibashi, H. *Org. Lett.*, 2009, 11 (15), 3298–3301.
10. Inoue, H.; Tamura, S. *Chem. Commun*. **1986**, 858-859.
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^{i} 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.
12. Gallagher, T.; Pardoe, D. A.; Porter, R. A. *Tetrahedron Lett*. **2000**, *41*, 5415-5418.
13. Benati, L.; Montevecchi, P. C. *J. Org. Chem*. **1981**, *46*, 4570-4573.
14. Katz, L.; Karger, L. S.; Schroeder, W.; Cohen, M. S. *J. Org. Chem*. **1953**, *18*, 1380-1402.

