Tetrahedron Letters, Vol. 34, No. 7, pp. 1085-1086, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

THE SYNTHESIS OF DITHYREANITRILE

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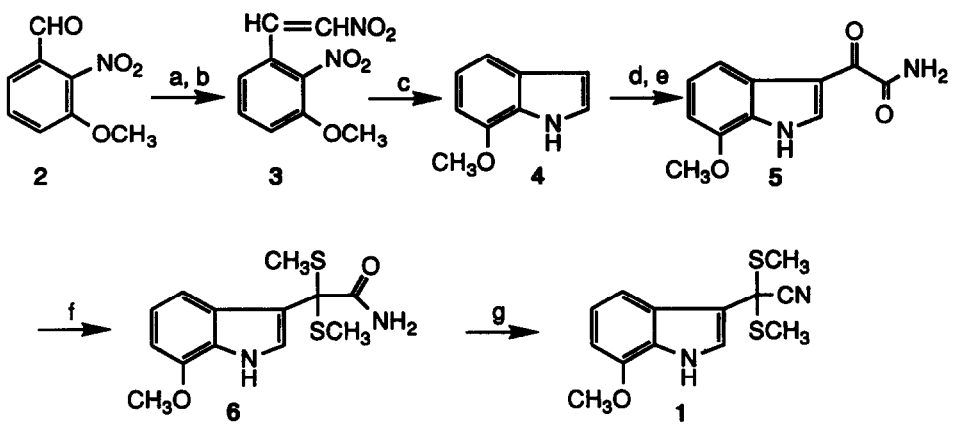
Summary: An efficient synthesis of dithyreanitrile (1), a novel insect antifeedant, is presented.

We recently reported the structure and biological activity of dithyreanitrile (1).[1] This unusual compound was isolated from the seeds of the crucifer *Dithyrea wislizenii*, and in biological assays with the fall armyworm and the European corn borer larvae, it demonstrated potent antifeedant activity. Our interest in the synthesis of 1 centered on its biological activity and the uncommon bis(methylthio)cyano methyl group in the 3-position of the indole ring.

While several routes were developed for the synthesis of the bis(methylthio)cyano methyl group, the most efficient and high yielding route for preparation of the natural product is shown below.[2]



(a) CH_3NO_2, CH_3OH, 9.5 N NaOH, 5-10 °C, 1 h; (b) $(CH_3CO)_2O$, $CH_3CO_2^-Na^+$, reflux, 5 min; (c) H_2, 10% Pd/C, $CH_3CO_2CH_2CH_3$, CH_3CO_2H; (d) $(COCl)_2$, Et_2O, 0 °C, 1 h; (e) conc. NH_4OH, 0 °C, 1 h; (f) TMS-SCH_3, BF_3•OEt_2, CH_3CN, 40 °C, 3 h; (g) pyridine, $POCl_3$, 0 °C, 1.5 h.

Commercially available 3-methoxy-2-nitrobenzaldehyde (2) was converted to 7-methoxyindole (4)[3] via the 3-methoxy-2,β-dinitrostyrene (3)[4] according to the procedure of Kalir.[5] The conversion of 4 to 7-methoxyindole-3-glyoxylamide (5) was based on the synthesis of N,N-dimethyl-7-methoxyindole-3-glyoxylamide also reported by Kalir.[5] A cold solution of 4 (1.215 g, 8.27 mmole) in anhydrous ether (~5 mL)

was treated with a solution of oxalyl chloride (1.23 mL, 14 mmole) in anhydrous ether (~3 mL) and stirred for 1 h at 0 °C. The red-orange 7-methoxyindole-3-glyoxylyl chloride which resulted was filtered from the reaction mixture, immediately added to cold conc. NH_4OH (~20 mL), and stirred for 1 h at 0 °C. The reaction mixture was filtered, and the precipitate was dried overnight under vacuum to yield 1.664 g (92%) of **5**[6] as a pale yellow solid.

A warm (~40 °C) solution of **5** (0.252 g, 1.16 mmole) in dry acetonitrile (~62 mL) was treated with TMS-SCH_3 (0.50 mL, 3.5 mmole) and BF_3•OEt_2 (0.15 mL, 1.2 mmole) and stirred for ~3 h at ~40 °C.[7] The reaction was quenched by the addition of H_2O. The majority of the solvent was removed by rotary evaporation. Treatment of the residue with ether (~50 mL) and H_2O (~45 mL) followed by filtration yielded 0.277 g (81%) of **6**[8] as a white crystalline solid.

The procedure for the dehydration of **6** was taken from a report on the conversion of bis(ethylthio)-acetamide to bis(ethylthio)acetonitrile.[9] A cold solution of **6** (0.220 g, 0.74 mmole) in dry pyridine (~1.3 mL) was treated with $POCl_3$ (0.1 mL, 1 mmole) and stirred for 90 min at 5-10 °C. The reaction mixture was poured into ice-water (~8 mL), acidified with 2 N HCl to a pH 2, and then extracted with ether (4 x 7 mL). The ether extracts were combined, dried over $MgSO_4$, and filtered. Removal of the solvent yielded a yellow oil which was chromatographed over SiO_2 with 3:1 hexanes:ethyl acetate to yield 0.167 g (81%) of **1**[10] as a white crystalline solid.

With a suitable synthesis for the generation of **1** in hand, further investigations of the biological activity of dithyreanitrile and its analogues can be undertaken.

Acknowledgments. This work was partially supported by NIH CA24487.

References and Notes

1. Powell, R.G.; Mikolajczak, K.L.; Zilkowski, B.W.; Lu, H.S.M.; Mantus, E.K.; Clardy, J. *Experientia* **1991**, *47*, 304-306.
2. Mantus, E.K. Ph.D. Dissertation, Cornell University, 1991.
3. **4**: yield 61%; ^{1}H NMR ($CDCl_3$) δ 3.99 (s, 3H, OCH_3), 6.57 (m, 1H), 6.68 (d, 1H, J=8 Hz), 7.08 (t, 1H, J=8 Hz), 7.18 (m, 1H), 7.31 (d, 1H, J=8 Hz), 8.43 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 55.2, 101.6, 102.7, 113.4, 120.1, 123.7, 126.3, 129.1, 146.1.
4. **3**: yield 72%; mp 152-153 °C (lit.[5] mp 155-157 °C); ^{1}H NMR ($CDCl_3$) δ 3.94 (s, 3H, OCH_3), 7.19 (d, 2H, J=8.3 Hz), 7.50 (m, 2H), 7.86 (d, 1H, J=13.7 Hz); ^{13}C NMR ($CDCl_3$) δ 56.7, 115.7, 119.2, 123.8, 131.6, 131.8, 140.5, 141.2, 151.6.
5. Kalir, A.; Balderman, D.; Edery, H.; Porath, G. *Isr. J. Chem.* **1967**, *5*, 129-136.
6. **5**: mp 205.0-205.5 °C (dec); ^{1}H NMR (DMSO-d_6) δ 3.93 (s, 3H, OCH_3), 6.83 (d, 1H, J=8 Hz), 7.16 (t, 1H, J=8 Hz), 7.70 (br s, 1H), 7.78 (d, 1H, J=8 Hz), 8.06 (br s, 1H), 8.52 (s, 1H), 12.36 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 55.4, 104.3, 112.7, 113.8, 123.4, 126.1, 127.7, 137.2, 146.4, 165.9, 182.9; exact mass calcd for $C_{11}H_{10}N_2O_3$: 218.0691; found 218.0693. Anal. Calcd for $C_{11}H_{10}N_2O_3$: C, 60.55; H, 4.62; N, 12.84; O, 22. Found: C, 60.54; H, 4.58; N, 12.68; O, 22.03.
7. Evans, D.A.; Truesdale, L.K.; Grimm, K.G.; Nesbitt, S.L. *J. Am. Chem. Soc.*, **1977**, *99*, 5009-5017.
8. **6**: mp 195-200 °C (dec); ^{1}H NMR (DMSO-d_6) δ 1.78 (s, 6H, 2 x SCH_3), 3.89 (s, 3H, OCH_3), 6.66 (d, 1H, J=8 Hz), 6.75 (br s, 1H), 6.87 (t, 1H, J=8 Hz), 7.22 (m, 3H), 11.25 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 12.4, 55.2, 67.4, 102.0, 112.7, 113.1, 119.2, 124.2, 126.0, 126.9, 146.1, 171.4; exact mass calcd for $C_{13}H_{16}N_2O_2S_2$: 296.0653; found: 296.0670. Anal. Calcd for $C_{13}H_{16}N_2O_2S_2$: C, 52.68; H, 5.44; N, 9.45; O, 10.8; S, 21.63. Found: C, 52.76; H, 5.45; N, 9.53; O, 10.31; S, 21.33.
9. Gonzalez, J.; Sanchez, F.; Torres, T. *Synthesis* **1983**, 911-913.
10. Spectroscopic data of **1** were identical to that of the isolated natural product.1: mp 132-134 °C (dec); ^{1}H NMR ($CDCl_3$) δ 2.28 (s, 6H, 2 x SCH_3), 3.96 (s, 3H, OCH_3), 6.69 (d, 1H, J=8 Hz), 7.10 (t, 1H, J=8 Hz), 7.45 (d, 1 H, J=3 Hz), 7.67 (d, 1H, J=8 Hz), 8.45 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 15.7, 48.2, 55.4, 102.9, 110.3, 113.6, 117.2, 120.8, 124.0, 124.9, 127.9, 146.2; exact mass calcd for $C_{13}H_{14}N_2OS_2$: 278.0548; found: 278.0555. Anal. Calcd for $C_{13}H_{14}N_2OS_2$: C, 56.09; H, 5.07; N, 10.06; O, 5.75; S, 23.03. Found: C, 56.40; H, 5.10; N, 10.09; O, 5.46; S, 22.88.

(Received in USA 15 October 1992; accepted 2 December 1992)