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THE BIRCH REDUCTION OF THIOPHENE-2-CARBOXYLIC ACID

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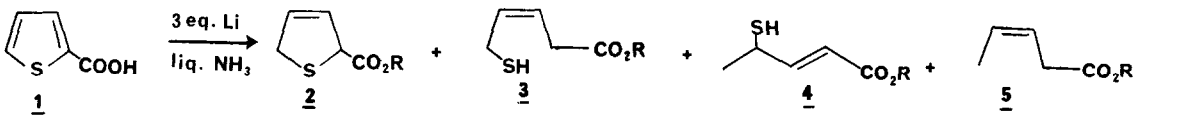
Abstract: *The Birch reduction of thiophene-2-carboxylic acid was investigated. The course of the reaction was controlled by altering the ratio of lithium to acid and by changing the proton source.*

Our initial interest in the synthesis of 2,5-dihydrothiophene-2-carboxylic acids led us to investigate the Birch reduction of thiophene-2-carboxylic acid (1). Although there are many mehtods available for preparing 2,5-dihydrothiophenes, the utilization of the Birch reduction for this purpose has, until recently,[1a-c] received little attention. The most common procedures for preparing 2,5-dihydrothiophenes involve ring closures,[2a-d] although one electrochemical method has been reported.[3]

We have found that the Birch reduction of 1, unlike that of furan-2-carboxylic acid,[4] does not afford a clean yield of the corresponding 2,5-dihydro derivative. A mixture of products is obtained, as illustrated in Scheme 1. The reduction is carried out by suspending 1 in liquid ammonia and adding three equivalents of lithium to the suspension in small



Scheme 1

2-5a, R = H
2-5b, R = CH_3

pieces over a period of several minutes. The deep blue color is allowed to persist for 5 min and the reaction is then quenched with ammonium chloride. The ammonia is evaporated, then the solid residue is dissolved in a minimum amount of water and acidified with 6 N hydrochloric acid. Extraction with chloroform followed by drying over magnesium sulfate, filtration, and removal of solvent in vacuo affords the mixture shown in Scheme 1. To facilitate identifi-

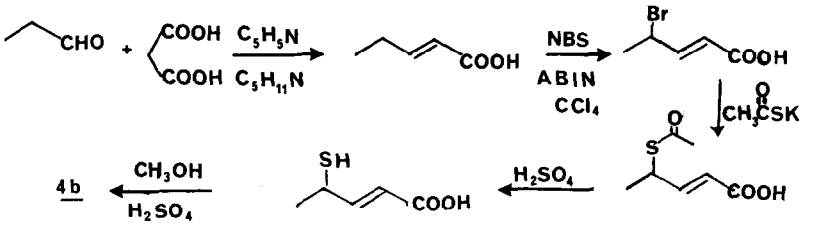
cation of the reduction products, the acids were converted to the corresponding methyl esters using either diazomethane in ether or methanol and an acid catalyst at ambient temperature, and analyzed by gas chromatography/mass spectrometry (10 ft x 1/4" O.D., 2 mm I.D., 10% Carbowax 20 M column; temperature program: 4 min at 70°, heating cycle of 4°/min to 220°, and 20 min at 220°; ionizing voltage: 70 eV, ion source temperature: 200-210°). Four major constituents with retention times of 9, 27, 29, and 31 min were separated.

The last peak (31 min, 78%) corresponds to methyl 2,5-dihydrothiophene-2-carboxylate (2b), ^{1}H NMR ($CDCl_3$): δ 3.73 (3H, s), 3.84 (2H, m), 4.83 (1H, m), 5.99 (2H, m); IR (neat) ν_{max} 1735 cm^{-1} (CO); ^{13}C NMR ($CDCl_3$): δ 172.2, 131.7, 127.2, 55.4, 52.5, 39.3; m/z (Rel %): 144 (75), 113 (12.5), 111 (47.6), 85 (100), 45 (55.7). The compound eluting at 29 min (9.5%) was identified by mass spectral and ^{1}H NMR data to be cis-methyl 5-mercapto-3-pentenoate (3b). ^{1}H NMR ($CDCl_3$): δ 1.5 (1H, t, J=7Hz), 3.15 (4H, m), 3.62 (3H, s), 5.62 (2H, m); IR (neat) ν_{max} 2530 (SH), 1740 (CO) cm^{-1}; m/z (Rel %): 146 (7), 115 (18), 114 (90), 113 (32), 87 (59), 86 (70), 85 (100), 83 (73), 81 (75), 71 (67), 59 (82), 55 (54), 54 (75), 53 (81). Compound 3b was found to decompose in the GC/MS interface (Watson-Biemann type[5]) if the temperature of the interface was above 200°. The product of this decomposition was methyl 2,4-pentadienoate (retention time 12 min).

The mass spectrum of the third compound, eluting at 27 min (7%), had a molecular ion of m/z 146, and was isomeric with 3b. The ^{1}H NMR of the compound exhibited a deshielded doublet at δ 7.02 (J_1=16Hz and J_3=7Hz) and the IR exhibited an α, β unsaturated carbonyl at 1720 cm^{-1}, indicating it to be trans-methyl 4-mercapto-2-pentenoate (4b); ^{1}H NMR ($CDCl_3$): δ 1.48 (3H, d, J=6.5Hz), 1.80 (1H, d, J=6.5Hz), 3.70 and 3.71 (m, s, 4H), 5.88 (1H, dd, J_1=16Hz, J_2=1Hz), 7.02 (1H, dd, J_1=16Hz, J_3=7.0Hz); IR (neat) ν_{max} 2510 (SH), 1720 (CO), 1650 (C=C) cm^{-1}; m/z (Rel %): 146 (13), 115 (25), 114 (100), 113 (80), 112 (18), 111 (12), 107 (25), 87 (40), 86 (38), 85 (15), 82 (44), 81 (69), 71 (31), 59 (56), 55 (54), 54 (25), 53 (71), 45 (31).

The structural assignment was confirmed by an unequivocal synthesis of an authentic sample of 4b as shown in Scheme 2.

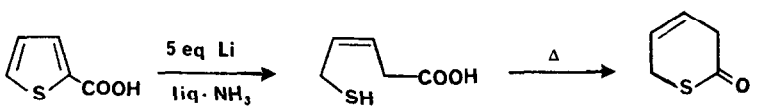
The compound eluting at 9 min (5%) was identified as cis-methyl 3-pentenoate (5b), its mass spectrum showing the molecular ion at m/z 114; ^{1}H NMR ($CDCl_3$): δ 1.70 (3H, m), 3.10 (2H, m), 3.67 (3H, s), 5.60 (2H, m); IR (neat) ν_{max} 1745 cm^{-1} (CO); m/z (Rel %): 114 (93), 99 (12), 83 (18), 82 (72), 72 (67), 59 (78), 55 (100), 54 (72), 53 (61), 39 (66), 29 (61). Since



Scheme 2

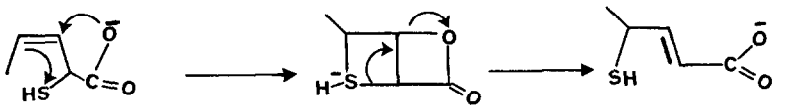
allylic sulfur is known to be cleaved under Birch reduction conditions,[6a,b] the corresponding acid was believed to be formed on further reduction of 3a. An authentic sample of 5b was prepared by treating 3a with W-2 Raney nickel in acetone, followed by esterification with diazomethane in ether.

When the Birch reduction of thiophene-2-carboxylic acid is carried out using five equivalents of lithium and methanol as the proton source, a single product was obtained, 5-mercapto-3-pentenoic acid, 3a.[1b,c] The geometry of the double bond was shown to be cis by conversion of the acid to the corresponding δ-thiolactone (6) on heating. The physical data also supported the cis geometry: ^{1}H NMR ($CDCl_3$): δ 3.10 (2H, m), 3.67 (2H, m), 6.05 (2H, m); IR (neat) ν_{max} 1660 cm^{-1} (CO); m/z (Rel %): 114 (5), 85 (22), 54 (100), 53 (17), 45 (21), 39 (27), 27 (13).



1 3a 6

Although 2a, 3a, and 5a are normal reduction products the presence of 4a was not expected. Another possible reduction product, 2-mercapto-3-pentenoic acid was not observed. It appeared possible that this product might be converted to 4a under the conditions of the reaction. A possible reaction pathway for 4a is shown in Scheme 3.



Sulfurane intermediate

4a

Scheme 3

The rearrangement shown is not unprecedented and seems plausible in view of earlier work implicating octet expansion in divalent sulfur.[7] Such a pathway is supported by the observed change of configuration from Z to E. A review of the literature for 2-mercapto-3-pentenoic acid showed that this compound was not previously known. We are currently investigating this interesting reaction further and are also exploring the utility of 3a in the synthesis of natural products containing cis double bonds.

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