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PREPARATION OF ALKYL ETHYNYL SULFIDES AND ALKYL E-2-IODOETHENYL SULFIDES

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Abstract: An efficient method for the preparation of multi-gram quantities of ethynyl sulfides is exemplified by the synthesis of ethynyl n.pentyl sulfide. Treatment of the latter with zirconocene chloride hydride/N-iodosuccinimide gave E-2-iodoethenyl n.pentyl sulfide in high yield and stereoselectivity. The latter compound rearranged to the Z isomer on storage at -20°C.

As part of our programme into the synthesis of thia analogues of natural products, we required multi-gram quantities of the alkynyl thioether ethynyl n.pentyl sulfide, and the E isomer of the corresponding iodoethenyl thioether. An investigation of the

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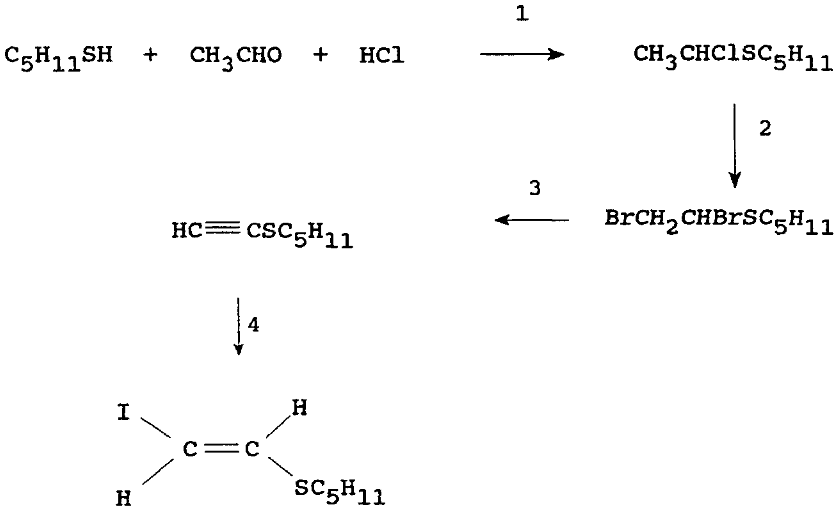
literature methods for the preparation of terminal alkynyl n.alkyl sulfides[2-5] revealed that none were satisfactory for the preparation of these compounds on a large scale, giving in our hands only low yields of impure products. Although t.butyl ethynyl sulfide can be obtained in low yield from Z-1,2-dichloroethylene and t.butylmercaptan,[6] this procedure did not give any of the desired acetylenic product when n.pentylmercaptan was used as the thiol reagent.

Our approach to the synthesis of ethynyl n.pentyl sulfide is outlined in the following Scheme and involved the 1-chloroethyl thioether intermediate prepared by earlier workers, followed by a one step conversion of this compound to the 1,2-dibromoethyl thioether.[1-4] The latter intermediate can be converted in good yield directly to the ethynyl thioether by dehydrohalogenation using sodium amide in liquid ammonia. Other methods for dehydrohalogenation of the dibromide (KOH, KOt.Bu, $PhNEt_2$ under various conditions both with and without phase transfer catalysis) gave mixtures or poor yields of acetylenic thioether.

The E-iodovinyl sulfide was prepared in high yield and stereoselectivity by hydrozirconation-iodination of the terminal acetylene.[7,8] The stereochemistry of the product was assigned by literature precedent for the



Scheme 1. -15°C, 82%; 2. Br_2/35°C, >90%; 3. $3NaNH_2/NH_3$/-40°C, 70%; 4. $ZrCp_2ClH$/NIS/THF/20°C, 90%

formation of E olefins during reduction of alkynes by these reagents,[7,8] and by the observation of a characteristic trans 14.3 Hz coupling between the olefinic hydrogens. Other methods for reductive iodination such as hydroalumination-iodination and hydroboration-iodination gave only low yields (20-30%) of the desired product.

The E isomer of 2-iodoethenyl n.pentyl sulfide was found to undergo clean rearrangement to the Z isomer during prolonged storage in solution at -20°C. Storage at room temperature led to sample decomposition. The Z isomer is characterized by a 7.1

Hz coupling between its olefinic hydrogens, and may be stabilized by a degree of hypervalent bonding between sulfur and iodine: analysis via the Alchemy™ modelling software reveals a structure with a sulfur-iodine internuclear distance of 3.04Å, compared with the sum of the Van der Waal's radii of 3.78Å.[9]

The reactions outlined above therefore represent the most convenient method for the preparation of ethynyl alkyl sulfides and E-2-iodoethenyl alkyl sulfides, and suggest that, although conditions for the rearrangement of E to Z 2-iodoethenyl alkyl sulfides have not been optimized, the latter compounds are also accessible by this route.

Experimental procedures:

1-Chloroethyl n.pentyl sulfide: A stirred mixture of acetaldehyde (44g) and 1-pentanethiol (20g) was saturated with HCl gas -20°C. A further 84g of thiol was then added dropwise at <-10°C, followed by HCl until saturation point. The mixture was then stirred at -10°C for 15 min and room temperature for 20 min before being extracted with pentane (4x50mL). The extract was dried, evaporated and distilled[10] (25cm Vigreaux column) at 39°C, 0.3mm, to give the product (80%).[11,12] ^{1}Hnmr 0.92 (t, CH_3), 1.26-1.41, 1.56-1.68 (m, CH_2's), 1.83 (d, CH_3CHCl), 2.62-2.88 (m, CH_2S), 5.26 (q, CHCl), ^{13}Cnmr 13.6, 22.1, 26.2, 28.4, 30.9, 31.9, 64.2. Anal. calcd. for $C_7H_{15}ClS$, C 50.43, H 9.06, S 19.23, Cl 21.27%. Found C 50.50, H 8.84, S 19.17, Cl 21.46%.

1,2-Dibromoethyl n.pentyl sulfide: Bromine (80g) was added to stirred 1-chloroethyl n.pentyl sulfide (83.4g) at such a rate that the temperature was maintained at 35°C. The mixture was stirred for 15 min. following completion of the addition, and then evaporated to give product (>90%) which was used directly in the next step. ^{1}Hnmr 0.91 (t, CH_3), 1.29-1.44, 1.61-1.71 (m, CH_2's), 2.63-2.82 (m, CH_2S), 3.84-4.07 (m, CH_2Br), 5.34 (dd, CHBr), ^{13}Cnmr 14.1, 22.1, 28.0, 30.8, 32.6, 35.5, 58.8.

Ethynyl n.pentyl sulfide: The above dibromide (145g) was added dropwise to a stirred suspension of sodium amide (68.3g) in ammonia (2L) at -40°C. The resulting mixture was stirred at reflux for 1h and the solvent then allowed to evaporate. Water was added, the product extracted into ether, and the dried extract evaporated and distilled[13] at 30°C, 1mm to give the product (70%).[14] ^{1}Hnmr 0.92 (t, CH_3), 1.33-1.43, 1.71-1.78 (m, CH_2's), 2.69 (s, CH), 2.74 (t, CH_2S), ^{13}Cnmr 13.8, 22.1, 28.8, 30.3, 35.1, 74.7, 81.6. Anal. calcd. for $C_7H_{12}S$, C 65.65, H 9.44, S 25.04%. Found C 65.69, H 9.50, S 25.10%.

E-2-Iodoethenyl n.pentyl sulfide: Ziconocene hydride chloride (0.584g) was added to a stirred solution of ethynyl n.pentyl sulfide (0.285g) in dry THF (10mL) at room temperature. The mixture was stirred for 20 min., N-iodosuccinimide (0.5g) was added, and stirring continued for a further 30 min. Hexane (10mL) was added, and the mixture washed (5% $NaHCO_3$, satd. NaCl), dried and evaporated. Flash chromatography (silica gel/ethyl acetate) then gave the product (90%). ^{1}Hnmr 0.90 (t, CH_3), 1.32-1.39, 1.60-1.67 (m, CH_2's), 2.70 (t, CH_2S), 5.90, 6.92 (each d, J = 14.3 Hz, =CH's), ^{13}Cnmr 13.9, 22.1, 28.8, 30.8, 32.5, 66.7, 136.4.

Z-2-Iodoethenyl n.pentyl sulfide: A sample of the above E-alkene in THF (25 mole %) was stored in the dark at -20°C. After 6 months the ^{1}Hnmr spectrum showed δ 0.90 (t, CH_3), 1.32-1.39, 1.64 (m, CH_2's), 2.70 (t, CH_2S), 6.23, 7.04 (each d, J = 7.1 Hz, =CH's).

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10. The distillation must be performed at <50°C to avoid loss of product by elimination of HCl.
11. The receiving vessel should be cooled to -10°C.
12. The chloroethyl thioether is stable for several months at -5°C.
13. The receiving vessel should be cooled to -30°C.
14. The ethynyl sulfide is stable for at least 8 months if stored at -20°C in the absence of oxygen.

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