[3+2]-Cycloaddition of 2-(*tert*-butylsulfanyl)propenoic acid derivatives to cyclooctyne

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Abstract

The title compounds **1a,b** being α-acceptor-substituted *tert*-butyl vinylsulfides add to cyclooctyne; upon warming dioxane solutions of **1a,b** for two days 2,3,4,5,6,7,8,9-octahydrocycloocta[*b*]thiophenes **7a,b** were formed in good yield, accompanied by loss of isobutene.

Keywords: Hydrothiophene synthesis, vinyl sulfides, cycloalkynes, sulfonium ylides

Introduction

Hydrothiophene-forming thermal [3+2]-cycloadditions of 2-*tert*-butylsulfanylpropenoic acid derivatives, like nitrile **1a** and ester **1b**, to electron poor alkynes like **2** have been reported by us earlier (Scheme 1).[1,2] Analogous reactions are given by the corresponding 2-*tert*-butylselanyl compounds.[3] The reactions have been interpreted in terms of the intermediacy of stabilized five-membered cyclic sulfonium (or selenonium) ylides[1-3] (as **3a,b**) which, in turn, loose isobutene and thereby form the final dihydrothiophenes **4a**,**b** (or -selenophenes).


a R = CN
b R = CO$_2$CH$_3$
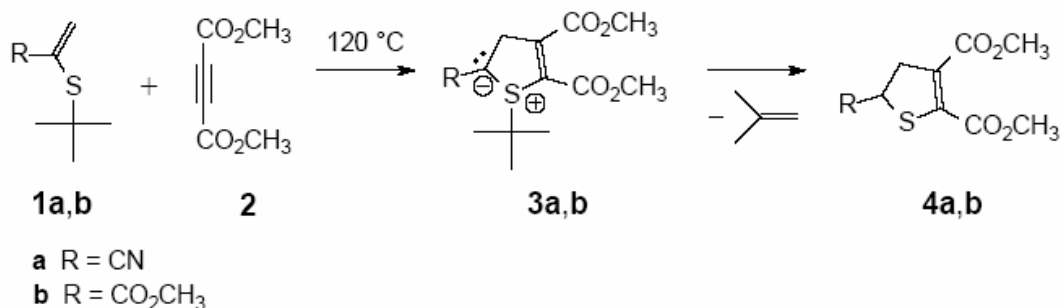
Scheme 1

If alkyl groups other than *tert*-butyl are attached to the sulfur (or selenium) atom, elimination

of that residue in the form of an alkene is either impossible or retarded, and other reactions ensue.[2,3] Related but bicyclic and unstabilized sulfonium ylides have been invoked in the reaction of 2,3-dihydrothiophenes with dimethyl ethynedicarboxylate.[4]

Preparative Work and Discussion

We wondered whether a cyclic alkyne, being activated by ring strain rather than by electron demand, would also undergo the above reaction. Cyclooctyne (**5**), readily accessible from cyclooctene,[5] was treated with a 40% excess of each of 2-(*tert*-butylsulfanyl)-propenonitrile (**1a**)[6] and methyl 2-(*tert*-butylsulfanyl)propenoate (**1b**)[7] in dioxane solution at reflux temperature for 60 or 48 h, respectively (Scheme 2). Excess starting materials were separated off chromatographically.

a R = CN
b R = CO$_2$CH$_3$
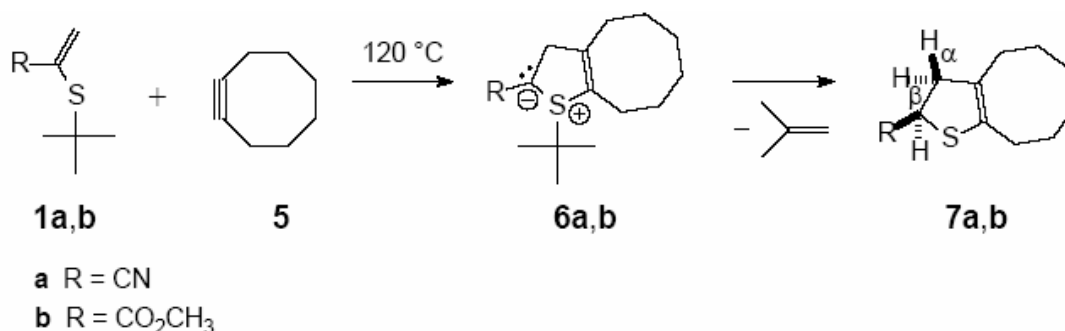
Scheme 2

The ^{1}H NMR spectra of the purified products lacking the *tert*-butyl singlets of the starting materials immediately made evident that a reaction had occurred. The presence of ABX-patterns for the dihydrothiophene ring protons 3-H$_\alpha$, 3-H$_\beta$ (AB) and 2-H (X), and two groups of multiplets for four and eight protons representing the six methylene groups present in the eight membered ring clearly support structures **7a,b** of the products, which were obtained in above 80% yields. Elemental analyses and the mass spectra also support these structures. Again, ylides **6a,b** are proposed as logical intermediates, although at present it cannot be decided whether they are formed in a single step from the starting materials or via additional intermediates, for example biradicals or zwitterions. It should be noted that olefins like **1a,b** tend to form head-to-head [2+2]-dimers,[8] very likely via 1,4-biradicals. In principle, the latter could be precursors to the ylides **6a,b**. Also, it cannot be ruled out that ylides **6a,b** exist in an equilibrium with the starting materials.

Conclusions

Successful [3+2]-cycloadditions of two activated vinyl sulfides to cyclooctyne have been carried

out. These cases as well as the analogous [3+2]-cycloadditions of **1a,b** to other alkynes including electron deficient and strained olefins[1,2,9,10] represent a $C_2S + C_2$ type thiophene ring synthesis using an electro-neutral C_2S-unit, while the most closely related $C_2S + C_2$ approach published earlier[11] employs alkynethiolates as C_2S components. From the number of successful examples it can be stated that the method employed in this study and in our previous investigations is fairly general.

Experimental Section

General Procedures. IR spectra were taken on a Perkin-Elmer 983 instrument. ^1H and ^{13}C NMR spectra ($CDCl_3$ as solvent, TMS as internal standard) were recorded on a Bruker DRX 500 instrument (500 MHz for ^1H). Elemental analyses were carried out on a Carlo Erba Model 1106 Elemental Analyzer. The mass spectra were recorded on a double focusing AMD 604 spectrometer in the EI Mode at 70 eV ionization energy, the samples were evaporated at 120 °C. Preparative Layer Chromatography (PLC): Glass plates (48 cm x 20 cm) were coated with silica gel Merck PF_{254} (applied as an aqueous slurry and air-dried affording a 1 mm layer). Zones were detected by indicator (fluorescence quenching upon 254 nm illumination) and – after removal from the plates – were extracted with ethyl acetate.

Starting materials: 2-(*tert-B*utylsulfanyl)propenonitrile (**1a**) was prepared according to Gundermann and Thomas,[6] bp 79 °C/17 mbar; n= 1.4800 (lit.[6] bp 67–68 °C/12 Torr; n_{20D}= 1.4802). Methyl 2-(*tert*-butylsulfanyl)propenoate (**1b**) was prepared according to lit.,[7] bp 79 °C/15 Torr; n= 1.5020 (lit.[7] bp 92–93 °C/12 Torr; n= 1.4795). Cyclooctyne (**5**) was prepared according to lit.,[5] bp 52 °C/16 Torr; n= 1.4880 (lit.[5] bp 50–55 °C/20 Torr; n= 1.4876).
2,3,4,5,6,7,8,9-Octahydrocycloocta[*b*]thiophene-2-carbonitrile (**7a**). A mixture of 2.54 g (0.018 mol) of 2-(tert-butylsulfanyl)propenonitrile (**1a**), 1.08 g (0.010 mol) of cyclooctyne (**5**), and 10 mL of dioxane was kept at 120 °C for 2.5 d and concentrated. The brown residue was subjected to bulb-to-bulb distillation at 140 °C/0.02 mbar to yield a yellow oil, which was separated by PLC on 6 plates using petroleum ether/diethyl ether 3:1. The intense zone with R_f = 0.50 was collected and redistilled as above (120 °C/0.02 mbar) to give 1.56 g (0.008 mol, 81%) of a yellow oil **7a**, n= 1.5462. ^1H NMR (500 MHz): ABX [δ_A = 3.14 (3-H_β), δ_B = 2.97 (3-H_α), δ_X = 4.20 (2-H) $|^2J_{AB}|$ = 15.9 Hz, $^3J_{AX}$ = 8.9 Hz, $^3J_{BX}$ = 4.7 Hz, the signals of H_A are additionally split by ^4J = 1.1 Hz], δ 2.35–2.20 (m, 4H, 4- and 9-CH_2), 1.68–1.42 (m, 8H, 5-, 6-, 7-, 8-CH_2); ^{13}C NMR: δ 131.47 (C-9a), 127.67 (C-3a), 120.64 (CN), 44.78 (C-3), 32.03 (C-2), 28.65, 28.36, 27.17, 26.41, 26.01, 25.75 (all CH_2); IR (KBr): [cm^{-1}] 2923 and 2851 (CH_2), 2236 (CN), 1460 and 1444 (s), 1357, 1331, 1311, 1279, 1262, 1248, 1230, 1175, 1093, 1026, 885, 775, 690; MS: *m/z* (%) 193 (M+, 86), 166 (16), 165 (100), 151 (32), 150 (38), 140 (36), 139 (14), 138 (52), 137 (64), 125 (49), 124 (17), 123 (15), 122 (15), 112 (13), 111 (23), 110 (11), 107 (17), 97 (23), 93 (20), 91 (20), 84 (13), 79 (29), 77 (18), 67 (14), 65 (14), 59 (24), 45 (17), 41 (36), 39 (20). Anal.

calcd. for $C_{11}H_{15}NS$ (193.31): C, 68.35; H, 7.82; N, 7.25; S, 16.69. Found: C, 68.20; H, 7.75; N, 7.30; S, 16.83.

Methyl 2,3,4,5,6,7,8,9-octahydrocycloocta[*b*]thiophene-2-carboxylate (7b). A mixture of 3.17 g (0.018 mol) of methyl-2-(*tert*-butylsulfanyl)propenoate (**1b**), 1.08 g (0.01 mol) of cyclooctyne (**5**), and 10 mL of dioxane was kept for 2 d at 120 °C and concentrated. Bulb-to-bulb distillation (140 °C, 0.02 mbar) gave a clear liquid, which was further separated by PLC on 10 plates using petroleum ether/diethyl ether (3:1). The material contained in the intense zone at $R_f = 0.45$ gave, after bulb-to-bulb distillation (130 °C, 0.02 mbar) 1.85 g (0.008 mol, 82%) of a pale yellow oil **7b**, n= 1.5324. ^{1}H NMR (500 MHz): δ 3.74 (s, 3H, OCH$_3$), ABX [δ$_A$ = 3.15 (3-H$_α$), δ$_B$ = 2.94 (3-H$_β$), δ$_X$ = 4.21 (2-H), $|2J_{AB}|$ = 16.2 Hz, $3J_{AX}$ = 9.9 Hz, $3J_{BX}$ = 5.5 Hz; additional signal splittings due to long range couplings: 3-H$_α$: 0.6 Hz, 3-H$_β$: 0.8 Hz, 2-H: 1.0 Hz]; 2.30–2.16 (m, 4H, 9- and 4-CH$_2$), 1.58–1.26 (m, 8H, 5-, 6-, 7-, 8-CH$_2$); ^{13}C NMR: δ 173.14 (C=O), 129.97 (C-9a), 128.37 (C-3a), 52.39 (O*C*H$_3$), 45.65 (C-2), 28.75, 28.31, 27.33, 26.24, 26.06, 25.73 (all CH$_2$); IR (Film): [cm^{-1}] 2923, 2849, 1740 (C=O), 1459, 1434, 1398, 1329, 1303, 1249, 1231, 1206, 1168, 1069, 1027, 985, 885; MS: *m/z* (%) 226 (M$_+$, 65), 198 (65), 193 (51), 171 (13), 168 (12), 167 (71), 166 (12), 165 (13), 140 (14), 139 (11), 138 (15), 137 (14), 133 (17), 125 (17), 122 (35), 111 (35), 110 (11), 107 (22), 99 (14), 98 (11), 97 (100), 91 (18), 79 (16), 77 (13), 67 (11), 57 (21), 55 (15), 45 (12), 41 (27). Anal. calcd. for $C_{12}H_{18}O_2S$ (226.34): C, 63.68; H, 8.02; S, 14.17. Found: C, 63.55; H, 8.04; S, 14.24.

Acknowledgements

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