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# An Approach to 8-, 16- and 24-Membered Sulfur-containing Heterocycles *via* Homolytic Cycloaddition of Alkynes with Butane-1,4-dithiol

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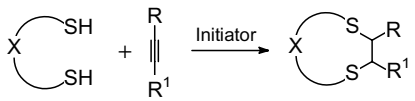
Homolytic cycloaddition of butane-1,4-dithiol with alkynes offers a facile one-pot route to 8-membered 1,4-dithiocanes and 16- and 24-membered crown thioethers, 1,4,9,12-tetrathiacyclohexadecanes and 1,4,9,12,17,20-hexathiacyclotetracosanes.

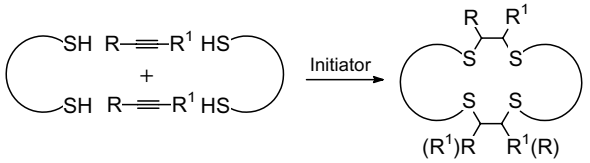
Homolytic cycloaddition of α,ω-dithiols with alkynes (Scheme 1) has been successfully used in the synthesis of 6- and 7-membered 1,4-dithiacyclanes[1–3] as well as 9-, 12-, 14-, 18- and 21-membered crown thioethers.[4,5] This approach to the construction of cyclic systems extends the employment in organic synthesis of such well-known and currently highly popular free radical reactions as intramolecular cyclization[6] and macrocyclization,[7] Scheme 1.




X = $(CH_2)_2$, $(CH_2)_3$, $(CH_2CH_2)_2O$, $(CH_2CH_2OCH_2)_2$
Initiator: $Pr_3B$-$O_2$, AIBN

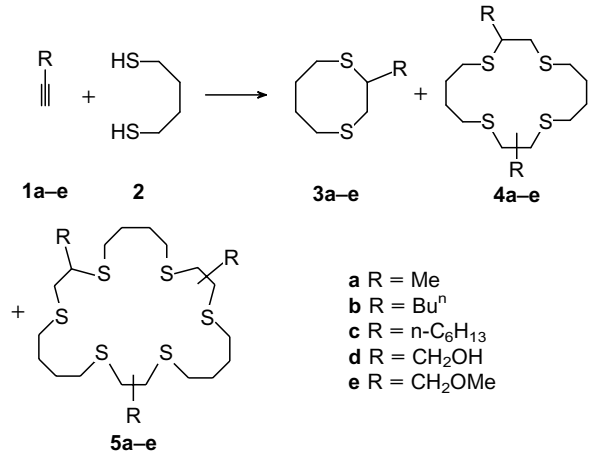
**Scheme 1**

Similar to "classical" free radical cyclization the efficiency of homolytic cycloaddition strongly depends on the size of the cyclic system to be synthesized according to this approach. In contrast to the readily accessible 6- and 7-membered 1,4-dithianes and 1,4-dithiepanes,[1–3] related 9-membered 1-oxa-4,7-dithiacyclononanes were formed only in a low yield.[5] Simultaneously with the decrease of the yield of 1:1 cycloadducts the contribution of parallel homolytic cycloaddition reactions leading to the formation of 2:2 and 3:3 cycloadducts (Scheme 2; only 2:2 cycloadducts are shown) increased.[3,5]




**Scheme 2**

To expand the scope of the strategy developed in the present work we have studied homolytic cycloaddition of alkynes **1a–e** with butane-1,4-dithiol **2** induced by free radical initiators [tripropylborane in the presence of oxygen or azobis(isobutyronitrile), AIBN]. It was found that this reaction resulted in the formation of 1:1 cycloadducts (1,4-dithiocanes **3a–e**) and two types of crown thioethers: 16-membered 2,10(11)-disubstituted 1,4,9,12-tetrathiacyclohexadecanes **4a–e** and 24-membered 2,10(11),18(19)-trisubstituted 1,4,9,12,17,20-hexathiacyclotetracosanes **5a–e** as 2:2 and 3:3 cycloadducts of homolytic cycloaddition–macrocyclization (Scheme 3).




**Scheme 3**

The yields of preparatively-isolated sulfur-containing heterocycles **3–5** are presented in Table 1.

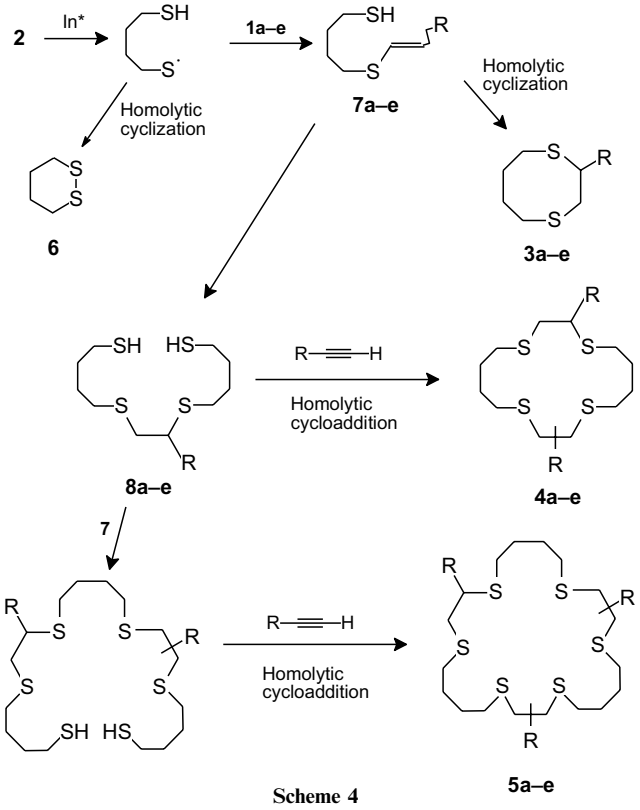
**Table 1** Homolytic cycloaddition of alkynes with butane-1,4-dithiol induced by tripropylborane.

| Alkyne | R | Products and yields (%) | | |
|---|---|---|---|---|
| **1a** | Me | **3a** (6) | **4a** (3) | **5a** (4) |
| **1b** | Bu | **3b** (2) | **4b** (9) | **5b** (2) |
| **1c** | $C_6H_{13}$ | **3c** (1) | **4c** (8) | **5c** (11) |
| **1d** | $CH_2OH$ | **3d** (3) | **4d** (9) | **5d** (3) |
| **1e** | $CH_2OMe$ | **3e** (2) | **4e** (6) | **5e** (2) |

It was found that in all experiments the starting butane-1,4-dithiol **2** was readily cyclized into 6-membered 1,2-dithiane **6**, the yield of which usually reached ~ 15%. The contribution of this highly competitive side-reaction increased on diminishing the reaction temperature and the yield of **6** exceeded 20% when the reaction was carried out at −70 °C. The yields and the ratio of **3–5** hardly depended on the concentration of starting reactants **1** and **2** (in the interval 0.05–0.4 mol $dm^{-3}$). The reaction appeared to be sensitive to the nature of free radical initiator and in the reaction of **1c** with **2** initiated by AIBN a practically inseparable mixture of products was formed containing, along with **3c–5c**, several other components of unidentified structure as well.

In all experiments a substantial part of the starting substrates was also converted into open-chain oligomeric adducts. Attempts to suppress this undesirable process failed, which could probably have been expected because of the usually comparatively low rate of intramolecular cyclization leading to 8-membered cyclic systems.[8,9] It should be noted that, nevertheless, the 8-membered ring products were synthesized in good yields *via* intramolecular radical cyclization of unsaturated bromides possessing a silaketal tether.[10]

Similar to the mechanism considered in ref. 5 we assume that the heterocyclization studied occurs according to Scheme 4 (*cf*. also ref. 3).




**Scheme 4**

Open-chain 2:1 adduct BuCH=CHS$(CH_2)_4$SCH=CHBu **9** was also isolated from the reaction of **1b** with **2** the structure of which was proved by $^1$H NMR and mass spectral ($M^+$ 286) data. In agreement with our previous results[5] **9** was inert towards further addition of another molecule of **2** that confirms the key role of alternative 2:1 open-chain adducts **8a–e** in the formation of crown thioethers **4** and **5**.

Taking into account the "one-pot" synthetic protocol, readily available starting reagents, the complex structure of the reaction products and the complicated character of alternative synthetic approaches to heterocycles of these types,[9,11,12] one may conclude that even the moderate yields of 8-, 16- and 24-membered sulfur-containing heterocycles and crown thioethers achieved here by application of the concept of homolytic cycloaddition can be considered as quite acceptable.

A typical procedure was as follows. A solution (4 ml, 1 mol $dm^{-3}$) of tripropylborane (4 mmol) in hexane was added to a solution of 0.49 g (4 mmol) of butane-1,4-dithiol **2**, alkyne **1** (4 mmol) and 0.65 ml (0.48 g, 16 mmol) of anhydrous MeOH in benzene (40 ml) under an argon

atmosphere. The reaction of **1c** with **2** induced by AIBN (5 mol% from **1c** and **2**) was carried out in benzene under reflux. All experiments were performed under TLC and GLC control. After complete consumption of dithiol **2** the reaction mixture was washed with an aqueous solution of KOH (5 ml, 1 mol $dm^{-3}$) and the benzene layer was separated. The aqueous layer was extracted with hexane ($3 \times 10$ ml), the extract was combined with the benzene layer, dried over $MgSO_4$ and evaporated *in vacuo*. The reaction products were isolated from the residue by chromatography on a column with $SiO_2$ (100–160 mesh). In the case of reaction of **2** with **1c** hexane–ether (40:1) was used as eluent. To isolate the products of the reactions of **2** with **1a** and **1d** the systems hexane–ether–methanol (3:0.2:0.1) and hexane–ether–methanol (1:4:0.1) were used, respectively. The structures of preparatively-isolated 1,4-dithiocanes **4**, 16- and 24-membered crown thioethers **5** and **6** were established on the basis of $^1H$ and $^{13}C$ NMR spectroscopy and mass spectrometric data.†

† *Spectroscopic data* for preparatively isolated reaction products: **3a**: $^1H$ NMR (250 MHz, $CDCl_3$) δ 1.34 (d, 3H), 1.64–1.83 (m, 4H), 2.37–3.00 (m, 7H); $^{13}C$ NMR (200 MHz, $CDCl_3$) δ 20.43, 28.50, 30.02, 31.05, 31.80, 38.36, 39.42; MS (chemical ionization) *m*/*z* 87 (100%), 161 (94), 129 (68), 163 (42), 55 (41), 218 (30), 121 (19), 177 (18), 120 (18), 162 ($M^+$, 17), 202 (15), 88 (14), 117 (13), 100 (11), 220 (10).

**3b**: $^1H$ NMR (250 MHz, $CDCl_3$) δ 0.90 (t, 3H), 1.20–1.60 (m, 6H), 1.60–2.00 (m, 4H), 2.50–3.00 (m, 7H); $^{13}C$ NMR (200 MHz, $CDCl_3$) δ 14.03, 22.57, 28.33, 28.87, 30.08, 32.63, 33.26, 38.35, 39.12, 45.80; MS (GLC-MS) *m*/*z* 204 ($M^+$, 100%), 87 (56), 120 (52), 56 (29), 103 (27), 157 (25), 88 (22), 45 (18), 116 (17), 44 (16), 115 (14), 101 (14), 135 (13), 60 (12), 61 (11), 122 (7), 102 (7), 121 (6), 86 (5), 147 (4), 81 (4).

**3c**: $^1H$ NMR (250 MHz, $CDCl_3$) δ 0.80–1.00 (t, 3H), 1.20–1.50 (m, 10H), 1.90–2.10 (m, 4H), 2.70–3.10 (m, 7H); $^{13}C$ NMR (200 MHz, $CDCl_3$) δ 14.04, 22.55, 26.96, 28.85, 29.08, 29.67, 31.66, 31.84, 33.28, 36.11, 39.06, 47.58; MS (electron impact) *m*/*z* 232 ($M^+$, 100%), 120 (99.5), 87 (92), 55 (62), 103 (45), 88 (37), 185 (30), 135 (27), 89 (23), 101 (22), 41 (24), 233 (18), 102 (14), 115 (13), 45 (13), 73 (12), 122 (11), 186 (3).

**3d**: $^1H$ NMR (250 MHz, $CDCl_3$) δ 1.75–2.25 (m, 4H), 2.30–2.50 (br.m, 1H, OH), 2.60–3.25 (m, 7H), 3.40–3.70 (m, 2H); $^{13}C$ NMR (200 MHz, $CDCl_3$) δ 25.91, 26.06, 29.32, 31.77, 35.18, 50.47, 64.19; MS (chemical ionization) *m*/*z* 178 ($M^+$, 100%), 87 (70), 55 (48), 120 (44), 89 (32), 61 (25), 45 (25), 73 (23), 147 (20), 59 (19), 47 (17), 57 (16), 119 (13), 46 (11), 121 (10), 85 (8), 103 (7), 122 (6), 74 (4), 106 (3), 177 (2), 127 (2).

**3e**: $^1H$ NMR (250 MHz, $CDCl_3$) δ 1.70–2.10 (m, 4H), 2.70–3.20 (m, 6H), 3.30–3.60 (m, 6H); $^{13}C$ NMR (200 MHz, $CDCl_3$) δ 26.35, 29.24, 29.72, 30.30, 31.67, 35.55, 58.76, 75.38; MS (electron impact) *m*/*z* 192 ($M^+$, 100%), 87 (98), 71 (89), 147 (78), 120 (77), 55 (72), 45 (69), 105 (55), 73 (53), 41 (52), 88 (50), 61 (38), 103 (38), 101 (34), 104 (33), 193 (32), 121 (31), 194 (30), 75 (29), 47 (27).

**4a**: $^1H$ NMR (250 MHz, $CDCl_3$) δ 1.35 (d, 6H), 1.65–1.85 (m, 8H), 2.25–3.00 (m, 14H); $^{13}C$ NMR (200 MHz, $CDCl_3$) δ 20.36, 28.48, 28.55, 30.19, 32.17, 39.39, 39.69; MS (chemical ionization) *m*/*z* 87 (100%), 129 (77), 161 (76), 177 (61), 55 (48), 120 (37), 89 (32), 163 (28), 41 (25), 58 (24), 324 ($M^+$, 23), 81 (21).

**4b**: $^1H$ NMR (250 MHz, $CDCl_3$) δ 0.88 (t, 6H), 1.20–1.55 (m, 12H), 1.60–1.90 (m, 8H), 2.45–2.85 (m, 14H); $^{13}C$ NMR (200 MHz, $CDCl_3$) δ 13.88, 22.45, 28.48, 28.57, 28.65, 28.90, 29.00, 30.10, 30.16, 31.27, 31.89, 31.94, 33.32, 33.59, 37.25, 38.14, 38.27, 44.75, 45.84, 46.02; MS (chemical ionization) *m*/*z* 408 ($M^+$, 100%), 163 (87), 203 (77), 205 (73), 177 (25), 409 (22), 89 (17), 407 (16), 219 (16), 410 (16), 121 (15), 87 (11), 303 (8), 191 (7), 120 (5), 81 (5), 117 (4), 165 (3), 222 (3).

**4c**: $^1H$ NMR (250 MHz, $CDCl_3$) δ 0.80–0.95 (m, 6H), 1.20–1.60 (m, 20H), 1.70–1.90 (m, 8H), 2.50–2.95 (m, 14H); $^{13}C$ NMR (200 MHz, $CDCl_3$) δ 14.02, 22.54, 26.75, 26.83, 28.54, 28.67, 28.71, 28.95, 29.08, 30.19, 30.43, 31.31, 31.63, 31.94, 32.01, 33.65, 33.93, 37.27, 38.18, 38.31, 44.74, 44.80, 45.90, 46.09; MS (electron impact) *m*/*z* 120 (100%), 87 (80), 152 (79), 55 (59), 89 (47), 233 (38), 199 (36), 464 ($M^+$, 28), 163 (27), 88 (22), 43 (23), 41 (23), 231 (21), 185 (16), 145 (13), 135 (11), 232 (11).

**4d**: $^1H$ NMR (250 MHz, $CDCl_3$) δ 1.60–1.90 (m, 8H), 2.40–3.00 (m, 16H), 3.55–3.90 (m, 4H); $^{13}C$ NMR (200 MHz, $CDCl_3$) δ 28.04, 28.46, 30.70, 31.56, 31.97, 34.12, 34.59, 48.00, 48.90, 63.66, 63.71, 63.79, 63.87; MS (chemical ionization) *m*/*z* 87 (100%), 120 (99), 152 (90), 121 (69), 56 (53), 179 (50), 89 (41), 356 ($M^+$, 31), 147 (25), 60 (23), 73 (19), 45 (19), 299 (17), 57 (17), 161 (16), 133 (13), 122 (12), 298 (11), 154 (10), 160 (9), 338 (9).

**4e**: $^1H$ NMR (250 MHz, $CDCl_3$) δ 1.60–1.90 (m, 8H), 2.70–3.00 (m, 12H), 3.30–3.60 (m, 12H); MS (chemical ionization) *m*/*z* 87 (100%), 120 (69), 193 (60), 121 (56), 71 (51), 152 (48), 384 ($M^+$, 45), 147 (42), 56 (40), 89 (26), 73 (21), 119 (18), 385 (17), 191 (16), 159 (16), 88 (16), 115 (14), 135 (13), 105 (12).

**5a**: $^1H$ NMR (250 MHz, $CDCl_3$) δ 1.40 (d, 9H), 1.65–1.90 (m, 12H), 2.25–3.00 (m, 21H); $^{13}C$ NMR (200 MHz, $CDCl_3$) δ 20.44, 28.68, 28.76, 30.29, 32.41, 39.58, 39.86; MS (chemical ionization) *m*/*z* 161 (100%), 87 (72), 129 (50), 120 (39), 152 (36), 194 (20), 162 (18), 145 (13), 115 (12), 75 (11), 131 (10), 147 (9), 41 (8), 149 (7), 486 ($M^+$, 6), 324 (6), 189 (6).

**5b**: $^1H$ NMR (250 MHz, $CDCl_3$) δ 0.90 (t, 9H), 1.30–1.55 (m, 18H), 1.65–1.90 (m, 12H), 2.50–2.90 (m, 21H); $^{13}C$ NMR (200 MHz, $CDCl_3$) δ 14.01, 22.57, 27.48, 27.65, 27.70, 28.02, 28.26, 28.69, 28.75, 29.19, 29.50, 29.65, 30.51, 30.57, 32.02, 33.30, 33.40, 37.83, 38.14, 38.20, 38.30, 38.43, 45.44, 45.50, 45.66, 45.70.

**5c**: $^1H$ NMR (250 MHz, $CDCl_3$) δ 0.80–0.95 (m, 9H), 1.25–1.55 (m, 30H), 1.65–1.90 (m, 12H), 2.45–2.90 (m, 21H); $^{13}C$ NMR (200 MHz, $CDCl_3$) δ 14.08, 22.62, 26.73, 28.49, 28.65, 28.80, 28.91, 29.17, 30.48, 31.72, 32.29, 32.50, 33.70, 38.21, 38.35, 45.83; MS (electron impact) *m*/*z* 696 (100%), 501 (20), 464 (20), 413 (14), 351 (24), 248 (47), 232 (88), 162 (29), 86 (35), 73 (24).

**5d**: $^1H$ NMR (250 MHz, $CDCl_3$) δ 1.55–2.00 (m, 12H), 2.30–2.55 (m, 3H, OH), 2.55–3.05 (m, 21H), 3.58–3.90 (m, 6H); $^{13}C$ NMR (200 MHz, $CDCl_3$) δ 28.18, 28.53, 30.67, 32.27, 34.62, 48.60, 63.51; MS (chemical ionization) *m*/*z* 87 (100%), 56 (51), 120 (45), 121 (41), 152 (40), 177 (38), 179 (34), 89 (34), 161 (30), 88 (23), 73 (22), 210 (19), 147 (18), 119 (17), 61 (14), 163 (13), 85 (11), 146 (10), 105 (10), 115 (10), 81 (9), 299 (8), 211 (8), 350 (7), 178 (7), 154 (7), 194 (6), 516 ($M^+$–$H_2O$, 5), 357 (5).

**5e**: $^1H$ NMR (250 MHz, $CDCl_3$) δ 1.60–1.90 (m, 12H), 2.70–3.00 (m, 18H), 3.30–3.45 (m, 18H); $^{13}C$ NMR (200 MHz, $CDCl_3$) δ 28.40, 28.57, 31.05, 32.41, 34.65, 45.53, 59.01, 74.30; MS (electron impact) *m*/*z* 151 (100%), 125 (97), 127 (80), 126 (79), 576 ($M^+$, 76), 135 (76), 179 (71), 138 (67), 141 (65), 167 (64), 163 (57), 193 (54), 183 (53), 155 (53), 152 (50), 164 (40), 225 (39), 107 (35), 192 (28), 384 (14), 306 (14).

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