Synthesis of Macrocyclic and Medium-ring Dithia Compounds using Caesium Thiolates

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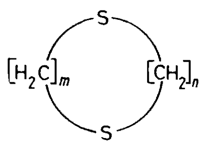
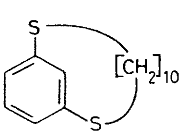
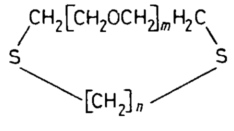
Summary The caesium salts of αω-dithiols react in dimethylformamide with αω-dihalides to give in good yield dithia medium-ring and macrocyclic compounds.



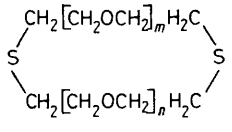
(1) $m = n = 5$
(2) $m = 3, n = 4$
(3) $m = 5, n = 10$
(4) $m = n = 10$



(5)



(6) $m = 3, n = 5$
(7) $m = 3; n = 10$



(8) $m = n = 3$
(9) $m = 3, n = 1$

Caesium salts have proved useful for the synthesis of a number of macrocyclic compounds.[1–4] We now report an application of caesium salts in the preparation of large rings containing sulphide linkages. Such compounds are of much interest as ligands of defined shape and bonding properties for transition metal ions[5] and for investigations of electron-transfer between sulphur atoms as well as of new types of sulphur–sulphur bonding.[6]

Syntheses have been described of various 'thia-crown' macrocycles[5,7] as well as of sulphur-containing cyclophanes wherein a combination of the 'rigid group principle'[8] and high dilution techniques[9] is put to advantage.[5,10] The synthetic principle used is S_N2 substitution by thiolate on a suitably activated carbon atom; this approach applied to conformationally very flexible molecules usually leads to at best moderate, and most often poor, yields of macrocycles.†

Results obtained using caesium thiolates for the syntheses of compounds (**1**)—(**9**), chosen to test the scope of the method, are shown in the Table. Deprotonation of the thiol in dry dimethylformamide (DMF) is rapid relative to subsequent reactions.

Compounds (**1**)[7e] and (**2**)[6a] have been reported previously in, respectively, 0·8% and 5·8% yields. Use of the caesium salt approach leads clearly to substantial improvement in yield of these nonpolar compounds. The yields of thia-crown ethers are also significantly increased: (**8**), for example, has been prepared in 20% yield (using Na_2CO_3 in EtOH)[7d] and (**9**) in 29% yield.[7c] The yields reported in the Table have not been fully optimized nor have all possible combinations of reactants leading to each product been examined. The reactants must be purified to ensure success of the reactions. All products are pure as established by spectroscopic methods but in some cases, especially (**3**) and (**4**), the removal of traces of nonpolar higher molecular weight compounds required medium pressure liquid chromatography (m.p.l.c.).

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† The various approaches and associated problems are discussed in ref. 7(e).

TABLE. Reaction of $\alpha\omega$-dithiols with $\alpha\omega$-dibromides in the presence of Cs_2CO_3 in DMF.

Reactants	Method[a]	Product (isolated yield)
$HS[CH_2]_5SH + Br[CH_2]_5Br$	A	**(1)** (63%)[b]
$HS[CH_2]_3SH + Br[CH_2]_4Br$	A	**(2)** (45%)[c]
$HS[CH_2]_{10}SH + Br[CH_2]_5Br$	A[d]	**(3)** (90%)[e]
"	B	**(3)** (80%)
"	C	**(3)** (45%)
$HS[CH_2]_{10}SH + Br[CH_2]_{10}Br$	A	**(4)** (85%)[f]
Benzene-1,3-dithiol + $Br[CH_2]_{10}Br$	B	**(5)** (95%)[g]
$HS[CH_2]_5SH + BrCH_2[CH_2OCH_2]_3CH_2Br$	B	**(6)** (85%)[h]
$HSCH_2[CH_2OCH_2]_3CH_2SH + Br[CH_2]_{10}Br$	A	**(7)** (85%)[i]
$HSCH_2[CH_2OCH_2]_3CH_2SH + BrCH_2[CH_2OCH_2]_3CH_2Br$	A	**(8)** (90%)[j]
$HSCH_2[CH_2OCH_2]_3CH_2SH + BrCH_2CH_2OCH_2CH_2Br$	A[k]	**(9)** (65%)[l]

[a] Method A: a magnetically stirred suspension of 1 mmol of Cs_2CO_3 in DMF (250 ml) was stirred at 50 °C under N_2. A solution containing 1 mmol each of dithiol and dibromide in DMF (50 ml) was added over 12—15 h. The DMF was removed *in vacuo* and the residue taken up in CH_2Cl_2, washed with H_2O, dried over $MgSO_4$, and purified. Method B: same as above except that Cs_2CO_3 (1 mmol) and dibromide (1 mmol) were put in DMF (250 ml) to which dithiol (1 mmol) in DMF (50 ml) was added over 12—15 h. Method C: a mixture of dithiol, dibromide, and Cs_2CO_3 (1 mmol each) in DMF (75 ml) was stirred under N_2 at 50 °C for 3 h. [b] Yield after recrystallization from MeOH, m.p. 78·5—80 °C (lit. [7e] 81—82·5 °C); yield before crystallization of ^1H n.m.r.-pure material 88%. [c] Yield after kugelrohr distillation at 0·006 mmHg, becomes solid: m.p. 56·5—58 °C (lit.,[6a] 58·5—60°C). [d] Essentially same yield obtained from the reaction of pentane-1,5-dithiol and 1,10-dibromodecane. [e] Analytical sample obtained by m.p.l.c. (n-hexane—CH_2Cl_2, 76:24), m.p. 71·5—72 °C; disulphone, m.p. 132—132·5 °C. [f] Analytical sample obtained by m.p.l.c. (n-hexane–CH_2Cl_2, 86:14), m.p. 48—49 °C; disulphone, m.p. 189—191 °C. [g] M.p. 103—105 °C; disulphone, m.p. 190—192 °C. [h] Liquid purified by kugelrohr distillation at 0·003 mmHg; disulphone, m.p. 110—111 °C; essentially same yield obtained using method A. [i] Liquid; disulphone, m.p. 75—78 °C; essentially same yield obtained using method B. [j] Liquid; disulphone, m.p. 87·5—89·5 °C; **(8)** has been reported in ref. 7(a). [k] Using 3-oxopentane-1,5-dithiol and 1,11-dibromo-3,6,9-trioxoundecane a 58% yield of **(9)** was obtained. [l] Yield after distillation, b.p. (0·6 mmHg) 170—175 °C [lit., [7c] b.p. (1 mmHg) 174—179 °C].

All the compounds reported here were characterized by ^1H n.m.r. spectra and the molecular compositions were established by osmometric molecular weights and elemental analyses or exact mass determinations, all values being in agreement with theory within experimental error. For all new compounds the crystalline disulphone derivatives were prepared in near quantitative yield by oxidation with an excess of *m*-chloroperbenzoic acid.

To examine the effect of the metal ions on the cyclisation, the yields of **(3)** were determined with Cs_2CO_3, Rb_2CO_3, K_2CO_3, Na_2CO_3, and $LiCO_3$ (method A, Table). The yields are respectively 90 (isolated), 84 (g.l.c.), 48 (g.l.c.), 33 (g.l.c.), and 0% (g.l.c.). These data emphasize again the beneficial effects of caesium ions (rubidium can also be effective although in our hands reaction products are less clean) coupled with a dipolar aprotic solvent like DMF [11] in promoting macrocycle formation.

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