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Direct Transformation of 1,3-Dihalides into Dithianes and Dithiepines via a Novel One-Pot Reaction with Carbon Disulfide and Sodium Borohydride

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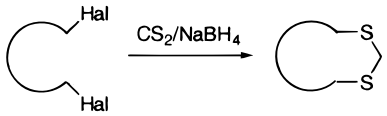
ABSTRACT



1,3-Dithianes and -dithiepines are prepared via an experimentally simple and efficient direct transformation of 1,*n*-alkyl dihalides utilizing carbon disulfide and sodium borohydride.

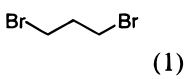
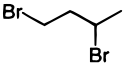
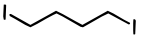
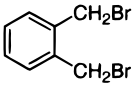
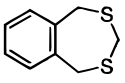
Cyclic dithioacetals, which are normally synthesized via acid-catalyzed reactions of 1,*n*-dithiols with ketones and aldehydes, are quite common in the chemistry of protecting groups.[1] With Corey and Seebach's reporting of 2-lithiodithiane additions to carbonyls three decades ago, cyclic thioacetals became even more ubiquitous as *synthons* utilized in many celebrated synthetic sequences.[2]

Recent findings in our laboratories[3] show that the dithiane moiety "as a whole" can also be used as photo-removable protection for carbonyl compounds. Along these lines we have been developing the photolytic C−C bond cleavage in dithiane−carbonyl adducts for what we tentatively dub *photo-take-apartable molecular objects*. This project required easy access to 1,3-dithianes substituted at a position other than 2 (mostly 5-substituted), which are not readily available through the existing thioacetal chemistry.

We therefore have developed and now report an experimentally simple one-pot *direct* transformation of alkyl dihalides into dithianes and dithiepines.

We have found that the reaction of sodium borohydride, CS_2, and an alkyl 1,*n*-dibromide or diiodide (3:1.5:1) furnishes the desired 1,3-dithiaheterocycles in moderate to good yields (Table 1).

Table 1

Dihalide	Product	Yield [a]
 (1)	 (2)	83%
 (3)	 (4)	36%
 (5)	 (6)	74%
 (7)	 (8)	79%

[a] General experimental procedure in THF.

Our mechanistic rationale includes double reduction of CS_2 by $NaBH_4$ leading to the formation of methane dithiolate,

(1) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley: New York, 1991; p 201.
(2) For a review see: Gröbel, B.-T.; Seebach, D. *Synthesis* **1977**, 357.
(3) McHale, W. A.; Kutateladze, A. G. *J. Org. Chem.* **1998**, *63*, 9924.

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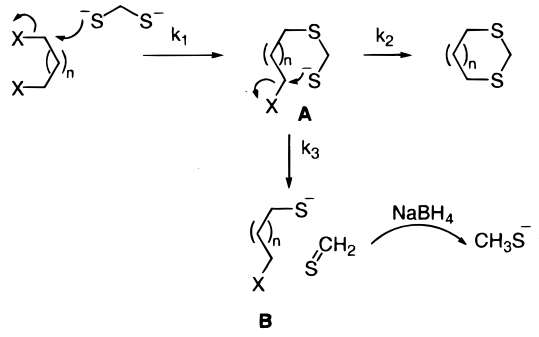
[$^{-}$S−CH_2−S^{-}],[4,5] which then displaces the halogens via a two-step (an inter- followed by an intramolecular) nucleophilic substitution, Scheme 1.

Scheme 1

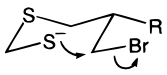


The timing of these two events is critical for a successful reaction to occur. If for some reason the intramolecular nucleophilic substitution (step k_2) is slow, a competing expulsion of thioformaldehyde from the intermediate **A** takes place ($k_2 < k_3$). Although we do not have direct evidence of CH_2═S formation, we isolated the products of the thiolate **B** reactions and detected traces of trithiane in the reaction mixtures. We also attribute detection of methyl sulfides in "failed" reactions to the presence of methylthiolate anion formed by further reduction of thioformaldehyde.

We will briefly discuss the two factors affecting the efficiency of this cyclization −the leaving group and the steric hindrance.

We found that dichloroalkanes as a rule do not produce the desired dithiaheterocycles. Only benzylic *o*-bis(chloromethyl)benzene gave a relatively good yield of benzodithiepine (**8**), although the dibromide reacted more efficiently (Table 1). When we used a mixed bromo-chloro substrate, 1-chloro-3-bromo-2-methylpropane, the intramolecular chlorine displacement step (k_2) was slow and the GC-MS analysis of the reaction mixture showed 3-chloro-2-methyl-1-propanethiol as the principal product. A 1,5-dihalide, β,β'-dichloroethyl ether, gave 1,4-thioxane, conceivably as a result of intramolecular cyclization in the intermediate of type **B** *after* thioformaldehyde expulsion.

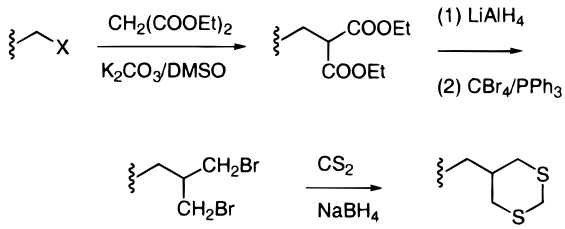
The reaction is found to be quite sensitive to steric impediments. A *secondary* bromide, 1,3-dibromobutane, produced 4-methyl-1,3-dithiane in a relatively modest yield (Table 1). Even reactions of *primary* 1,3-dibromides targeting 5-substituted 1,3-dithianes required a modification in our original technique to improve the yield. The less favorable k_2/k_3 ratio is probably due to the increased steric repulsion in the transition state, k_2, between the bromine atom (that is required to assume, at best, a gauche conformation) and the substituent R:



To improve the yields of 5-substituted dithianes, we utilized triglyme as a solvent: (i) aprotic solvents of higher polarity are known to enhance the efficiency of S_N2 processes and (ii) additionally, sodium borohydride is soluble in tryglime (see ref 9 for experimental details).

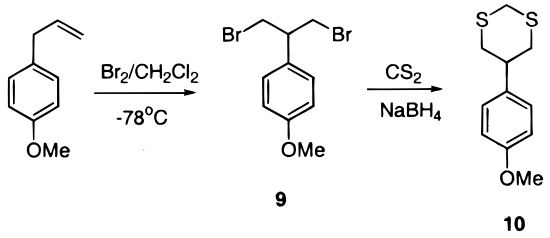
As it is mentioned above, our synthetic objective was to develop a simple method for preparation of dithianes tethered to each other or to other molecular objects via the position 5. One of the possible approaches to such systems, that we are currently developing, utilizes classic malonate chemistry, Scheme 2.[6]

Scheme 2



Another useful technique for 1,3-dibromide synthesis, which we identified for this study, makes use of phenonium ion rearrangement accompanying the electrophilic bromination in allylbenzenes, Scheme 3. Costa et al.[7] reported that

Scheme 3



9 **10**

bromination of safrole produced about 35% of the rearranged 1,3-dibromide. Dubois group found that bromination of allylanisole in chloroform at room temperature produced 48:52 mixture of the rearranged and the 1,2-adduct.[8] We investigated this reaction further and found that bromination of *p*-allylanisole in methylene chloride at −78 °C furnishes the rearranged 1,3-dibromide **9** almost quantitatively (>10:

(4) One of the possible actual forms of such dithiolate was previously reported in the inorganic literature as pentasodium tetrakis(dithiomethylene)-borate, $Na_5[B(SCH_2S)_4]$: Diamantikos, W.; Heinzelmann, H.; Rath, E.; Binder, H. *Z.. Anorg. Allg. Chem.* **1984** *517*, 111.

(5) We also cannot completely rule out a stepwise mechanism whereby CS_2 is first reduced into dithiaformate anion, which replaces one halogen, and the resulting dithiaester is then reduced to give **A**.

(6) Specific details on the malonate-based systems will be reported in the full paper.

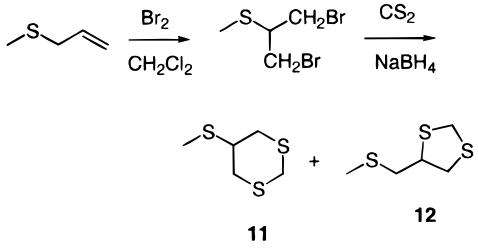
(7) Costa, P. R. R.; Rabi, J. A. *Tetrahedron Lett.* **1975**, 4535.

(8) Fain, D.; Dubois, J.-E. *J. Org. Chem.* **1982**, *47*, 4855.

1), which we used without additional purification in the next step to synthesize dithiane **10**, Scheme 3.[9] The rearranged 1,3-dibromide is a *kinetic* product of allylanisole bromination. It is known that upon equilibration at elevated temperatures and in the presence of Lewis acids it slowly interconverts into the 1,2-adduct with the equilibrium constant, $K = 10.1$, favoring the 1,2-adduct.[8] At room temperature and in the absence of Lewis acids, however, the 1,3-dibromide **9** that we synthesized did not show any reverse phenonium migration.

Allyl methyl sulfide is also known to rearrange quantitatively upon bromination.[10] Under our reaction conditions, a mixture of 5-(methylthio)-1,3-dithiane (**11**) and 4-(methylthiomethyl)-1,3-dithiolane (**12**) was obtained (Scheme 4).[11]

Scheme 4



We investigated the synthesis of 1,3-dithiolanes starting from vicinal dihalogenides. GC-MS analysis of the reaction with 1,2-dibromoethane showed 1,3-dithiolane as the major component of the reaction mixture. It appears, however, that the dithiolane ring is not stable under reaction conditions, and the isolated yields of dithiolanes were low.

In conclusion, we have developed a simple and inexpensive experimental procedure for direct transformation of 1,3- and 1,4-dihalides into 1,3-dithianes and dithiepines via reductive nucleophilic substitution with CS_2 and $NaBH_4$.[12] The technique has proven most valuable for the preparation of 5-substituted 1,3-dithianes.

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(9) Experimental details: 0.257 g (1.7 mmol) of allyl anisole was dissolved in 15 mL of methylene chloride and cooled to −78 °C. 0.278 g (1.7 mmol) of bromine in 5 mL of methylene chloride was added dropwise upon stirring. The reaction was allowed to warm to room temperature, the solvent was removed, and the residue was dissolved in 3 mL of triglyme and cooled to 0 °C. To this solution was added 0.197 g (5.2 mmol) of sodium borohydride followed by 0.198 g (2.6 mmol) of CS_2. The reaction turned yellow instantaneously. The reaction was stirred overnight at room temperature, at which point it was diluted with aqueous ammonium chloride, extracted with ether (3 × 10 mL), washed twice with brine, and dried over sodium sulfate. The solvent was removed, and the residue was column chromatographed (silica gel, 1: 20 ethyl acetate−hexane) to give 0.235 g (61% over two steps) of white solid (**10**). ^{1}H NMR (400 MHz, $CDCl_3$,δ) 7.1 (d, 2H, $J = 8.06$ Hz), 6.85 (d, 2H, $J = 8.06$ Hz), 4.08 (d, 1H, $J = 13.9$ Hz), 3.78 (s, 3H), 3.44 (d, 1H, $J = 13.9$ Hz), 3.16−2.95 (m, 3H), 2.78 (d, 2H, $J = 13.9$ Hz); ^{13}C NMR ($CDCl_3$, δ, DEPT-assignments) 158.245 (C), 137.349 (C), 127.355 (CH), 113.947 (CH), 55.233 (CH_3), 42.935 (CH), 35.884 (CH_2), 31.118 (CH_2) MS (*m*/*z*) 226 (M^+), 180, 179, 165, 164, 148, 134 (100%), 121, 119, 91, 77, 65, 51.

(10) Bland, J. M.; Stammer, C. H. *J. Org. Chem.* **1983**, *48*, 4393.

(11) As identified by GC-MS and NMR of reaction mixture. We failed to separate the two products; it appears that they interconvert on the slurry packed silica gel column.

(12) Dithianes and dithiapines synthesized in the present work via reductive nucleophilic substitution were previously described in the literature (see below). We characterized them by ^{1}H NMR, ^{13}C NMR, and mass spectroscopy: (a) 1,3-dithiane (**2**): ^{1}H NMR (400 MHz, $CDCl_3$, δ) 3.79 (s, 2H), 2.86−2.81 (m, 4H), 2.12−2.04 (m, 2H); MS (*m*/*z*) 120 (M^+, 100%), 105, 92, 87, 78, 74, 64, 59, 55, 51. (b) 4-methyl-1,3-dithiane (**4**):^{1}H NMR (400 MHz, $CDCl_3$, δ) 4.08 (d, 1H, $J = 14.04$ Hz), 3.53 (d, 1H, $J = 14.10$ Hz), 2.94−2.84 (m, 3H), 2.19−2.11 (m, 1H), 1.78−1.72 (m, 1H), 1.22 (d, 3H, $J = 6.92$ Hz); MS (*m*/*z*) 134 (M^+, 100%), 119, 106, 101, 87, 78, 73, 60, 55. (c) 1,3-dithiepane (**6**): ^{1}H NMR (400 MHz, $CDCl_3$,δ) 3.99 (s, 2H), 2.86−2.81 (m, 4H), 2.03−1.97 (m, 4H); ^{13}C NMR ($CDCl_3$, δ) 36.812 (CH_2), 32.543 (CH_2), 31.573 (CH_2); MS (*m*/*z*) 134 (M^+), 87 (100%), 78, 74, 60, 55, 51. (d) 1,5-dihydrobenzo[*e*]-1,3-dithiepine (**8**): ^{1}H NMR (400 MHz, $CDCl_3$,δ) 7.27−7.16 (m, 4H), 4.00 (s, 4H), 3.93 (s, 2H); ^{13}C NMR ($CDCl_3$, δ) 138.408 (C), 129.101(CH), 127.830 (CH), 38.480 (CH_2), 36.542(CH_2); MS(*m*/*z*) 182 (M^+), 135 (100%), 104, 97, 78, 63, 51. (1) Compounds **2**, **4**, **6**, **8**, **10** are described in (a) 1,3-dithiane (**2**): the material we obtained was identical with the authentic sample from Aldrich.1,3-dithiepane. (b) 4-Methyl-1,3-dithiane (**4**): Bulman Page, P. C. Klair, S. S.; Brown, M. P.; Smith, C. S.; Maginn, S. J.; Mulley, S. *Tetrahedron*, **1992**, *48*, 5933. (c) 1,3-Dithiepane (**6**): Semmelhack, C. L.; Chiu, I.-C.; Grohmann, K. G. *J. Am. Chem. Soc.* **1976**, *98*, 2005. (d) 1,5-Dihydrobenzo[*e*]-1,3-dithiepine (**8**): Sauriol-Lord, F.; St-Jacques, M. *Can. J. Chem.* **1979**, *57*, 3221. Smolinski, S.; Balazy, M.; Iwamura, H.; Sugawara, T.; Kawada, Y.; Iwamura, M. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 1106. (e) 5-(4-Methoxyphenyl)-1,3-dithiane (**10**): Yuichiro, H.; Nasato, N. *Liq. Cryst.* **1997**, *23*, 263.

(13) **General Experimental Procedure in THF.** A 20 mL solution of 5 mmol of dihalide and 7.5 mmol of CS_2 in dry THF was added at room temperature to a slurry of 15 mmol of sodium borohydride in 10 mL of THF, and the resulting solution was refluxed overnight. The reaction mixture was then worked-up with aqueous ammonium chloride, extracted with ether, and dried over sodium sulfate. The solvent was removed and the product purified by column chromatography (**4**, **6**, **8**, silica gel, ethyl acetate−hexane, 1:20) or recrystallization from methanol (**2**).